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CRANIOCEREBRAL WAR WOUNDS

OBSERVATIONS ON DELAYED TREATMENT

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THIS REPORT is based upon the experiences which we have encountered with severe head injuries, which have been admitted directly to a General Hospital in the North African Theater of Operations, or which have reached here through the usual channels of evacuation. There have been 130 cases of fracture of the skull, of which 74 have been battle casualties, and the remainder due to accidentally incurred injury. Although the number of cases of open head wounds which have been selected as a basis for this report is admittedly small, the cases which are cited illustrate some of the problems of treating this type of injury. Several case histories will be given in detail to demonstrate the fact that treatment, however long delayed, may still be expected to yield satisfactory results. We shall confine this report to facts which we ourselves have observed, and from which we have drawn certain conclusions.

EARLY TREATMENT

The aim of treatment of head wounds, like that of wounds of other regions, is multiple: First, the prevention or eradication of infection in open wounds; second, the preservation of function, or the improvement of physiologic defects resulting from the injury; third, the restoration of anatomic structure as completely as possible. Early and thorough definitive treatment with prompt conversion of a bleeding, contaminated, potentially infected, open wound, into a dry, clean, closed wound, remains the ideal for which to strive, and the following cases illustrate this point.

Case 1.—Age 23, a prisoner of war, was shot by a rifle bullet on August 10, 1943. At a Station Hospital 45 minutes after injury, a diagnosis of compound fracture of the right parietal bone was made. Sulfanilamide powder and dry dressings were applied, and the patient was transferred here 10 hours later. After shaving the head, examination showed a wound of entry in the posterior parietal region, with the wound of exit about 6 cm. anteriorly. From the wound of exit, there oozed brain and bloody fluid. Roentgenograms showed a comminuted fracture with multiple indriven fragments (Fig. 1). There was left hemiparesis. Operation was performed 13 hours after injury. After excision of the wound of entry and exit, a partial horseshoe skin flap was reflected,

exposing comminuted depressed fracture of the upper part of the parietal bone. Bone edges were rongeured and all loose bone was lifted out. There was a laceration of the dura, 3 cm. long by 1 cm. in width. Several fragments had penetrated to a depth of



FIG. 1.—Case 1: A, Lateral, and B, anteroposterior views showing fracture of the right parietal bone, with indriven comminuted bone fragments.

2 cm. All fragments and macerated brain tissue were removed. The involved area lay chiefly in the arm center. All bleeding points were coagulated. The dura was closed with temporal fascia transplant. The rest of the wound was closed in layers with silk, without sulfonamide or drainage. The postoperative course was smooth. The wound healed *per primam*. The patient was allowed up on the 10th day. Neurologic examination showed residual left facial weakness, and weakness of the left hand with loss of fine movements. He was transferred to the Prison Section on August 28. On October 15, 1943, reexamination showed considerable improvement in skilled movements of the left hand.

Case 2.—Age 23, was not a case of gunshot wound, but the problem involved differed not at all from that found in tangential perforating wounds. On September 1, 1943, he was struck in the head by the edge of a log protruding from a rapidly moving truck. At a Station Hospital the head was shaved, and sulfanilamide crystals and dry



FIG. 2.—Case 2: A and B. Extensive fracture of right parietal and frontal bones, outlined by arrows, with indriven bone fragments, and elevation of one large fragment (B).

dressings were applied to the compounded right frontal wound. He was treated for shock, and transferred to this hospital 20 hours later. Examination on admission showed a ragged laceration about 10 cm. long over the right frontoparietal region, from which bone fragments and brain were protruding (Fig. 2). There was left hemiplegia and inability to rotate eyes to the left. Twenty-one hours after injury, operation was performed by Major S. P. Harbison. After excision of the skin edges, the wound was extended inferiorly and superiorly, to obtain adequate exposure. Multiple bone fragments were removed; several fragments projected deep into the brain. Macerated brain tissue was sucked out to a depth of 4 cm. Hemorrhage was controlled with coagulation and muscle stamps. The dura was closed with temporal fascia transplant. The rest of the wound was sutured in layers with silk, without sulfonamide or drainage.

The first few days after operation were stormy, with periodic episodes of increased blood pressure and restlessness. Hypertonic fluids were used to good effect, with daily normal fluid intake being restricted to 1500-2000 cc. Beginning about six days after operation, the patient's course improved steadily, and he became oriented and rational. The wound healed *per primam*. Left hemiplegia persisted, but the left leg recovered sufficiently to allow the patient to start walking on the 26th day. The defect was depressed, soft, and pulsating freely. He was sent to the Zone of Interior on October 27, 1943.

Case 3.—A French soldier, age 31, was shot by a rifle on May 16, 1943, and reached this hospital one hour after injury. There was a perforating wound of entry in the left lower frontal region; the bullet traversed tangentially, coming out through the tragus and pinna of the left ear. Bleeding was profuse from both wounds. This right-handed patient was not unconscious and had no speech disturbance, astereognosis or apraxia. Except for hyperactive knee-jerks, neurologic examination was negative. Blood transfusion was prepared, and operation was begun three hours after injury. The wound edges were excised and the entry and exit wounds were connected by incision through skin and temporal muscle down to bone. Depressed, comminuted fragments of the frontal and temporal bones were lifted out. A dural tear was enlarged and the underlying macerated brain was sucked out. Bleeding was controlled by silver clips and muscle stamps. The dura was closed, and the remainder of the wound was sutured in layers with silk without drainage and without sulfonamide. The postoperative course was satisfactory. Head and ear wounds healed *per primam*. On June 2, 1943, 16 days after operation, neurologic examination was negative, the patient was up and about, and he was discharged to the French authorities.

Case 4.—Age 30, was injured by shell fragments on February 7, 1943. He was admitted to a British General Hospital three hours later, with a severe compound fracture of the left frontal bone, and bleeding from the left nostril. Immediate operation was performed, through a frontal skin flap. Fragments of frontal bone were removed and the frontal sinus was curetted out. Through a laceration of the dura, the damaged tip of the frontal lobe, "the size of a tangerine," was sucked out. All bleeding was controlled by coagulation. The dura was closed with a fascial transplant, and a muscle tampon was placed over a defect in the cribriform plate. Sulfanilamide powder was applied extradurally and the wound was closed without drainage. The patient was allowed up on the 12th day after operation, and evacuated to the rear on the 19th day. He arrived at this hospital on March 2, 1943. The left frontal wound was well-healed, and pulsated freely. There was complete amaurosis of the left eye with primary optic atrophy. Neurologic examination was otherwise negative. The patient was perfectly well until March 12, when he developed cerebrospinal rhinorrhea. He was kept in a sitting or upright position, fluids were forced, and sulfadiazine was given prophylactically. Rhinorrhea ceased on March 18. There were no signs of infection or aerocele, and he was discharged to the Zone of Interior on March 30, 1943.

In cases of acute head injury seen early by us, tight closure without drain-

age and without local sulfonamide has been the rule. Sulfadiazine is given orally or parenterally as prophylaxis only in those cases in which infection is suspected, particularly in wounds which communicate with the nasal or accessory sinuses, *e.g.*, Case 4.

Case 4 illustrates the effectiveness of early and thorough treatment of a severe head wound complicated by penetration of the frontal sinus and cribriform plate, and loss of dura. The treatment of the subsequent cerebrospinal leak followed well-established principles. Had the leak persisted, or had an increasing aerocele developed, secondary craniotomy would have been necessary.

DELAYED DÉBRIDEMENT

Patients with head wounds who may be expected to survive, tolerate transportation quite well, and delayed but thorough treatment is to be preferred to early incomplete measures. Early in the North African campaign we were faced with the necessity of doing long-delayed débridements. Since then we have found that this procedure may be expected to yield satisfactory results, although undoubtedly not as good as would ensue from more prompt definitive care. Conversely, we have been impressed with the complications that may arise if reliance is placed upon inadequate early treatment.

The establishment of any arbitrary time limit within which definitive therapy may be carried out is not necessary. Early débridement and closure should always remain our goal. However, it should be noted that, with the exception of the few cases with dangerous compression due to hemorrhage or a very large depressed fracture, hasty, urgent, inadequate surgery is not usually demanded in head wounds. Unless there is at hand a surgeon familiar with the technical aspects of the treatment of these injuries, and unless he has available sufficient equipment with which to control bleeding, plus satisfactory assistance and the facilities to care for these patients for several days after operation, it is questionable whether any radical procedure should be attempted. The desirability of having such equipment as suction, silver clips, and/or electrosurgical unit for hemostasis, cannot be over-emphasized.

In our series, there have been eight cases in which débridement with closure was done between 36 hours and four days after injury, with primary healing. Additional cases, some of whose records follow, were operated upon and closed after a much longer interval (one as late as 32 days) with surprisingly good results.

Case 5.—Age 29, was injured by a mortar shell fragment on March 24, 1943, sustaining a compound fracture of the left parieto-occipital region. On the day of injury, the wound was "débrided" at a Surgical Hospital, with removal of bone chips and copper fragment. Sulfanilamide was placed in the wound, and the galea and skin were closed in layers. The patient reached here on April 8, 1943. The left parieto-occipital wound was incompletely healed; there was one small area which communicated directly with underlying necrotic brain. There was early papilledema. The left pupil was larger than the right. Repeated visual field examinations by Capt. E. B. Alvis, revealed right homonymous hemianopsia with macular sparing on the right.

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Hyperreflexia with ankle clonus was present, without pathologic toe signs. There was minimal nominal aphasia; no alexia or agraphia. Roentgenograms showed multiple indriven fragments in the occipital region (Fig. 3). On April 14, (21 days after injury) operation was performed under local anesthesia. The entire incompletely healed scalp wound was excised. There was a long narrow bone defect through which necrotic brain extruded; this was enlarged to expose the edges of lacerated dura around the periphery. Necrotic brain, old blood clots, numerous bits of hair, and multiple small fragments of bone were gently sucked out until the edges of the lesion were reached. Several pieces of bone, with accompanying hair, were found to have perforated through the wall of the ventricle, and on removing them there was a gush of ventricular fluid. All damaged brain was removed. The defect involved most of the occipital

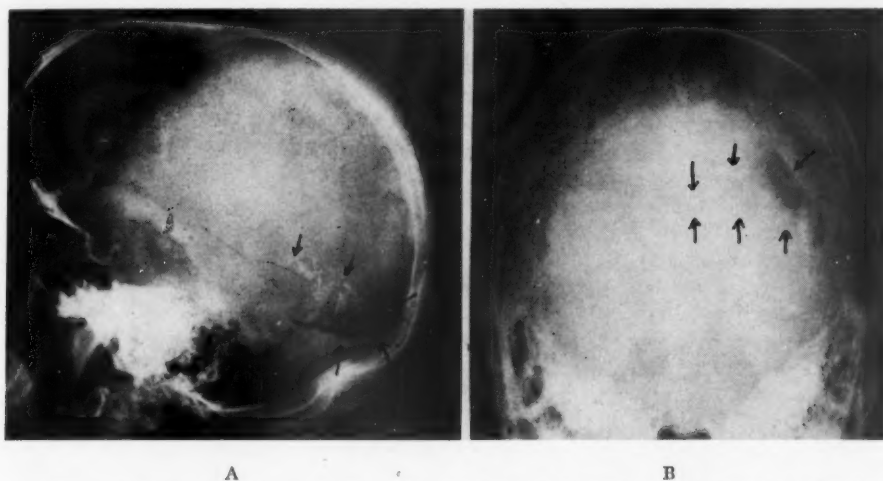


FIG. 3.—Case 5: A and B. Wound of left parieto-occipital region, with extensive destruction of occipital lobe by bone fragments (arrows) driven in to the midline. In this case, the ventricle was penetrated by loose bone and particles of hair. Delayed débridement, with tight closure, was carried out.

lobe, extending medially to the midline; inferiorly to the second temporal convolution; posteriorly only a small bit of brain tissue overlying the tentorium was uninvolved; anteriorly the defect extended to the posterior horn of the left lateral ventricle. Bleeding was controlled by hot saline packs. One large vessel near the surface was clamped and ligated with silk. After the field was dry, the defect was filled with saline. The thickened galea was split, giving an extra layer for suture, and the wound was closed without drainage.

The patient was given a course of sulfadiazine by mouth, and the postoperative course was perfectly smooth. The wound healed by first intention, and the papilledema subsided promptly. Examination after operation showed complete splitting of macular vision, but there was decrease in the blind spot on the left with some improvement in the peripheral field. All other neurologic abnormalities regressed and he was able to be up and around on the 10th day. He was discharged to the Zone of Interior on May 15, 1943.

Case 6.—Age 23, sustained a penetrating shrapnel wound of the right fronto-temporal region on March 24, 1943. "Débridement" was performed within three hours at a Treatment Station, where it was noted that brain tissue protruded from the wound. Sulfanilamide was applied and the wound was closed. At an Evacuation Hospital the next day, roentgenograms showed a metallic fragment in the left parietal region; this was wisely left alone. The patient reached here on March 31, 1943. The sutured wound of entry was infected and swollen. Neurologic examination was negative except

for a dilated right pupil, with ptosis and partial ophthalmoplegia. Roentgenograms showed a depressed bone fragment at the point of entry on the right, and a metallic foreign body at a depth of 5.5 cm. in the left parietal region. Because of the swollen wound and retained bone fragments, operation was performed on April 1, eight days after injury. The original wound was completely excised. Through a defect in the anterior part of the temporal muscle, a tract led down to the opening in the bone. Two pieces of bone were lifted out; beneath them lay false dura. Anteriorly unhealthy granulations and necrotic tissue were found and removed. Sulfanilamide crystals were sprinkled in the wound outside the false dura, and closure was done in layers, using fine catgut in this case for the temporal muscle and subcutaneous tissue.

The wound healed *per primam*. The third nerve palsy cleared rapidly. On April 4, the pupils were equal and reacted well; extraocular movements were well-performed, but some weakness of the levator palpebrae remained. The patient was discharged to the Zone of Interior on April 17, 1943.

Case 7.—Age 20, was struck by aerial bomb fragments on July 6, 1943. At an Evacuation Hospital, immediate débridement was done, with removal of bone fragments and necrotic brain, with primary closure. The wound of entry in the right frontotemporal region was small. Proptosis of the right eye developed. The patient arrived here on July 17, 1943. He was manic, irritable, and uncooperative; there was no power of reasoning or judgment. The slightest stimulus sent the man into a frenzy of screams and obscenity. His behavior was thoroughly uninhibited. There was a healed 5-cm. wound in the lower right frontal region. The bulbar conjunctiva was edematous and protruded between the lids. After retraction of the conjunctiva, the cornea was found to be cloudy, and vision in the right eye was absent. The left optic disk was hazy. Neurologic examination was otherwise negative. Roentgenograms (Fig. 4, A and B) showed a bony defect in the right frontotemporal region; the roof of the right orbit was crushed, and numerous bone fragments could be seen lying in the frontal lobe as well as within the orbit. There was a metallic foreign body near the surface of the left frontal lobe. There was no improvement during a week's observation.

On July 26, 1943, 20 days after injury, bilateral craniotomy through a Souttar incision was carried out (Fig. 4 C). The original wound of entry was used as one of the openings for the right bone flap. Extradural dissection was begun anteriorly. When the orbit was reached, a large dural defect was visualized, and necrotic brain welled up into the field. This was sucked out and the dissection was carried down to the optic chiasm. Many fragments of bone were found within the necrotic tip of the frontal lobe, and the roof of the orbit was shattered back to the optic foramen. These fragments were removed, relieving pressure on the orbital capsule. The optic nerve between the foramen and chiasm was intact. After the field was dry and clean, a transplant of temporal fascia was sutured in place to close the large dural defect. On the left side, exposure of the frontal lobe revealed adhesions between cortex and dura; on the surface of the cortex there was an area of yellow discoloration, in the center of which was a thin layer of necrotic brain covering the underlying foreign body. The fragment, together with the surrounding damaged brain, was excised *en masse*. The dura was sutured, and after replacing the bone flaps the wound was closed in layers with silk. Skin sutures were removed on the second day. The wound healed *per primam*, and the postoperative course was most gratifying. Proptosis disappeared. The patient became clear, rational, and cooperative; judgment, insight, and calculation were restored. He had no recollection of his earlier behavior. On August 17, the atrophic right eye was removed by Capt. Alvis. On September 6, 1943, he was returned to the Zone of Interior, with no demonstrable neurologic abnormalities. A letter written September 23, reported him to be in excellent state.

Case 8.—Age 21, was struck a glancing blow by a shell fragment on July 12, 1943. First treatment consisted of dressing, without débridement; he received sulfadiazine by

A



B



C

FIG. 4.—Case 7: A, lateral view, before operation, showing bone defect (wound of entry) in the inferior part of the right frontal bone. In B, postero-anterior view, roof of the right orbit is smashed and the orbit is filled with numerous bone fragments (arrow) many of which have penetrated the frontal lobe. The retained metallic foreign body is visualized in the left frontal lobe. C, postero-anterior view, after operation; the foreign body has been removed from the left frontal lobe, and the bone fragments have been removed from the right frontal lobe and orbit. (Compare with B). Outlines of the frontal bone flaps are seen.

mouth. The patient arrived here on July 26, with his original dressing in place. There was a dirty, sloughing wound of the left frontal region, about 4 cm. in diameter. Roentgenograms showed a comminuted, depressed fracture of the left frontal bone, with two small foreign bodies. The wound was so grossly contaminated that preliminary wet dressings were applied.

On July 28, operation was performed, with excision of the skin and débridement of the compound fracture. Bone fragments and the metallic foreign bodies were removed. An extradural clot, 1 cm. thick, was found over the anterior part of the frontal lobe, and was evacuated. The dura appeared to be intact, although it may have been torn originally. After repeated flushing with ether and saline, a thin layer of sulfanilamide was dusted on the dura. By means of a short releasing incision, the wound was closed without drainage. Postoperatively the patient received a course of sulfadiazine by mouth. On August 5, seven days after operation, the wound was completely healed except for a tiny area in the center which was not covered with epithelium, evidently due to too much tension. This area, about 2 Mm. long, was fully healed on August 10. On August 25, 1943, the patient was discharged to a Convalescent Hospital.

Case 9.—Age 30, a prisoner of war, was wounded about April 23, 1943. He was first seen at one of our Evacuation Hospitals on May 1, at which time was described a large, gaping wound of the left parietal region "obviously a week or so old." The wound was dusted with sulfanilamide and left open. He arrived here on May 11. Examination showed a 2-inch wound with infected cerebral hernia extruding. There was partial motor aphasia and right hemiparesis; no astereognosis. The herna was treated conservatively and became partially epithelized, but there continued to be a small amount of purulent drainage.

On June 14, the partially healed wound was completely excised to expose the edges of the bone defect. Through the defect, necrotic brain was sucked out down to intact tissue. Within the involved area were two small bone fragments. No frank pus was seen. After complete toilet of the wound, the scalp was mobilized by undermining and the galea and skin were closed in layers with silk. The wound healed *per primam*. Neurologically, there was slow improvement in speech and hemiparesis. The patient's mental agility was superb, and he was able to defeat his comrades and attendants regularly at chess. He remained in the Prison section until October 8, 1943, when he was repatriated as a walking case.

Case 10.—Age 26, was struck in the right parietal region by a bomb fragment on February 18, 1943. Because of the tactical situation, surgery could not be performed during his course of evacuation. He arrived here on March 2, 1943. Examination showed a tiny puncture wound in the right posterior parietal region, with sanguineo-purulent drainage. Roentgenograms showed a superficial metallic foreign body with a small depressed fracture. There was tenderness over an area 5 cm. in diameter. Neurologic examination was negative. On March 6, 1943, débridement was performed, with evacuation of bone fragments and a moderate amount of pus. The dura was intact. The wound was packed open with iodoform gauze. It granulated slowly, and secondary closure was done on April 8. The patient was evacuated to the rear on April 21, 1943, with his wound completely healed.

Case 11.—Age 23, received a shrapnel wound of the right parietal region on July 11, 1943. At a Provisional Surgical Hospital, the compound fracture was "débrided," and brain tissue removed. The wound was packed open with sulfanilamide powder and vaselined gauze. On July 20, he reached a Station Hospital where a firm pack was removed, revealing a cerebral fungus. There was early choked disk and left hemiparesis. The patient was operated upon by a neurosurgeon nine days after injury. After débridement, with removal of many bone fragments, sulfanilamide powder was sprinkled into the wound, and it was closed around a Dakin's tube. The wound healed promptly, and the patient was transferred to this hospital on August 9, 1943. The

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wound was well-healed. Eye grounds were normal. Left hemiparesis was slight. The patient continued to show steady improvement and he was sent to the Zone of Interior on August 17, 1943.

Case 12.—Age 23, received penetrating wounds of the head and abdomen from a land mine explosion on August 7, 1943. He was treated for shock, and celiotomy was performed four hours later at an Evacuation Hospital; there was no visceral perforation. His condition was too precarious for further surgery, and nothing was done to the left occipitoparietal wound except dressing with sulfanilamide and vaselined gauze. He was evacuated on August 12, and arrived here on August 29. *En route*, records of three medical installations noted exudation of pus and bone fragments from the wound. On admission here, there was blurring of the left optic disk with fullness of the

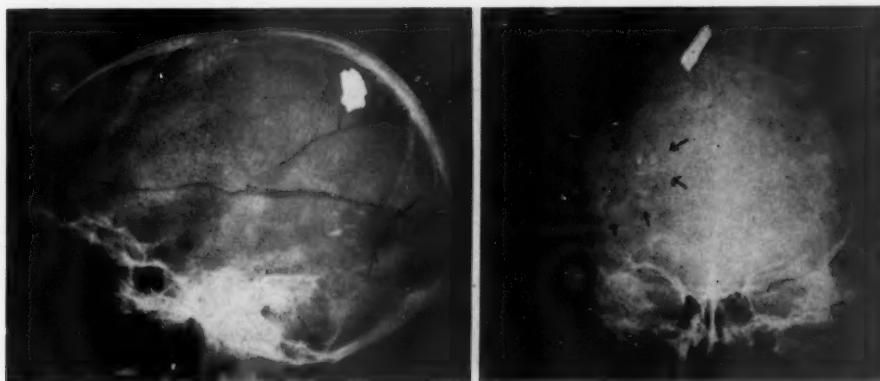


FIG. 5.—Case 12: A and B. Very extensive fracture with small wound of entry (arrow) in the left parieto-occipital region. Lines of fracture extend through the parietal to the anterior part of the frontal bone. There are two large fragments which have been elevated, and numerous smaller fragments driven deep into the occipital lobe. There is a large metallic foreign body just to the left of the midline. At operation, two pockets of pus were encountered, one around the metallic foreign body, and the other surrounding the indriven bone fragments. Treated by radical débridement and closure.

retinal vessels. There was right homonymous hemianopsia with some macular sparing. The patient was oriented, but had nominal aphasia, alexia, and agraphia. There was weakness of the extremities, with unsustained bilateral ankle and patellar clonus; and pathologic toe signs on the right. Position sense on the right was partially lost. In the left occipitoparietal region, there was a puffy, tender area, about 6 cm. in diameter, with a 2 x 3 cm. wound above the pinna of the ear. Foul, thick pus exuded through the wound. Roentgenograms showed extensive fractures of the left parietal and frontal bones; there were many bone chips driven deep into the brain beneath the defect, and a large metallic fragment in the region of the superior longitudinal sinus, just to the left of the midline (Fig. 5). While the patient was being built up generally, drainage from the wound continued. Repeated visual field examinations by Capt. Alvis, confirmed the macular sparing.

Transfusion was given preliminary to operation, which was performed on September 9, 32 days after injury. A left parieto-occipital skin-galeal flap was reflected, which included the draining entry wound near its center. Necrotic brain oozed from between multiple fractured fragments which were denuded of periosteum. The fragments were lifted out and bone edges rongeuired away until the peripheral edges of dura were exposed. Through the large dural defect, pus began to exude from the inferior as well as the superior portions of the parieto-occipital region. Surface vessels, of as yet intact areas of cortex, were coagulated and the entire lesion was uncapped. There was one large abscess in the lower part of the field. This was evacuated, and

from its depths multiple small bone fragments were removed. Another abscess lay superiorly. This was sucked out, and within its medial wall was found the metallic foreign body which was seen roentgenographically. The piece of metal touched the wall of the longitudinal sinus but had not penetrated it, and was removed. It was clear that the falx formed the medial boundary of the superior abscess. Between the two abscesses lay a mass of necrotic brain. This was removed by suction and found to extend to, but not through, the ventricle wall. Both abscess cavities and the intervening bridge of necrotic tissue were converted into a single saucer-shaped defect, 4 cm. wide, 7 cm. long, and 5 cm. deep, extending from above downward along the posterior part of the parietal lobe, with the falx medially and the petrous ridge inferiorly. Marsupialization would have been the procedure of choice on the basis of good surgical principles. However, since the approach had been made through a horseshoe-shaped incision, it was feared that a longitudinal incision through the center of the flap would jeopardize the blood supply of the anterior half. Accordingly, after toilet of the defect, the wound of entry was excised and closed, and the skin-galeal flap was sutured in layers, without local sulfonamide or drainage. It was thought that if abscess recurred, the entry wound could be reopened for drainage if necessary.

Sulfadiazine therapy was begun immediately after operation. The wound healed *per primam*. The postoperative course was uneventful and the patient was allowed up on the 10th day. The defect remained depressed and pulsated freely. Neurologically, there was slow but definite improvement. Blurring of optic disks disappeared. Visual fields showed no change. Visual acuity was 20/20 in both eyes. Nominal aphasia improved considerably. Alexia was marked but improved so that monosyllabic words could be read. There was definite acalculia. Skilled movements of the right hand were slightly less well-performed than on the left. Position sense of the arms was intact. The right lower extremity was slightly spastic with hyperactive knee jerk; no clonus or pathologic toe signs. Position sense of the right toes and ankle was absent. Fine discriminatory sense was absent over the entire right side of the body except for the head and neck; other sensation was intact. The heel-knee test was uncertain bilaterally. With the hands outstretched and eyes closed, the right arm drifted upward. The patient was able to walk well with eyes open; but with eyes closed, lack of position sense of right foot became apparent. He was discharged to the Zone of Interior on October 27, 1943.

Cases 5 (21 days), 6 (8 days), 7 (20 days), 8 (16 days), 9 (51 days), and 12 (32 days) are illustrative of what may be expected in some cases of head wounds even if they are allowed to go for a very long period of time before receiving adequate débridement, and are then subjected to radical débridement, with tight closure, without drainage. This is not to be misinterpreted as meaning that tight closure is the procedure of choice in all cases. The surgeon must apply his own judgment to each individual case. For example, in instances where there is gross infection and it is obvious that complete cleaning out of the wound cannot be accomplished, drainage is essential. The wound in Case 11 was closed around a Dakin's tube which was left for two days. In Case 10 the wound was packed open with iodoform gauze because of the extensive area of subcutaneous swelling and tenderness and the fear of spreading osteomyelitis. In this connection, it may be noted that, in our experience, spread of osteomyelitis in the skull is far less likely in battle wounds than in civilian practice where hematogenous infection occurs.

The good result in Case 5 is particularly significant in view of the long delay and the fact that the ventricle was penetrated by bone fragments and

hair. The procedure followed in Case 12 may be open to justifiable criticism. This defect presented every indication for drainage, containing as it did two pockets of pus and having discharged pus for over four weeks. The reasons for not draining have been given in the description, and through fortuitous circumstance, the case now stands as an extreme illustration of what may be accomplished with late débridement and tight closure in at least this instance.

As a rule, we have not used sulfonamide locally, even in late cases, but have given large doses parenterally and by mouth, checking blood concentrations daily. Usually, immediately after operation, the patient receives either six grams of sulfanilamide subcutaneously, or three grams of sodium sulfadiazine intravenously. The latter is repeated after four to six hours. In practically every case it has been possible to give one gram of sulfadiazine by mouth every four hours, beginning about 12 hours after operation. The six grams per day oral medication is continued for four days in the ordinary case (blood and urine being checked), after which time the dosage is decreased by two grams daily.

Emphasis should be placed upon adequate débridement. Débridement as a descriptive term is unhappily used somewhat loosely. The foregoing histories are a few that serve to illustrate the fact that incomplete débridement is usually ineffective. It is urged that, even if time is lacking, the surgeon should qualify the term débridement so that more rapid evaluation of the requirements of individual cases may be made as soon as they reach an installation where definitive surgery is available.

If débridement cannot be done adequately in early cases (and it should again be pointed out that physical facilities and equipment cannot be overestimated) it is better simply to shave the head and apply a snug, dry sterile dressing to the wound with sulfanilamide crystals superficially, and transport the patient to the rear, fortified with sulfonamide medication by mouth.

FASCIAL TRANSPLANTS

In our acute cases we have made every effort to restore anatomic relations whenever possible, and have used fascial or periosteal transplants when necessary to close dural defects. In later cases, unless one can be absolutely certain of the completeness of the débridement, it would appear to be unwise, and we have not closed the dura in such instances. The following cases, done elsewhere, are cited: The first with successful outcome; and the other two associated with complications.

Case 13.—Age 24, was struck in the left parietal region by a fragment of enemy antiaircraft shell on April 19, 1943. The wound was excised and metallic foreign body was removed at a Clearing Station two and one-half hours after injury. He was evacuated to a General Hospital (British) where a secondary débridement was done on April 21. A bone fragment and necrotic brain tissue were removed. A periosteal graft was used to close the dural defect and the wound was closed tightly in layers.

Recovery was uneventful. The patient arrived here on May 9, at which time neurologic examination was entirely negative, and the head wound was solidly healed. On May 15, 1943, he was sent to the Zone of Interior with the expectation of subsequent return to full combat duty.

Case 14.—Age 21, was struck in the right frontal region by enemy rifle fire on August 7, 1943. He was able to walk to an Aid Station, where his wound was dressed and he was given sulfanilamide. Due to local conditions, he did not reach a Field Hospital until August 9. Roentgenograms there revealed a right parietal fracture, with numerous foreign bodies at the site of fracture. He had a left hemiplegia, and brain tissue extruding from the wound. On August 10, three days after injury, operation was performed. After removal of macerated brain and bone fragments, the dura was

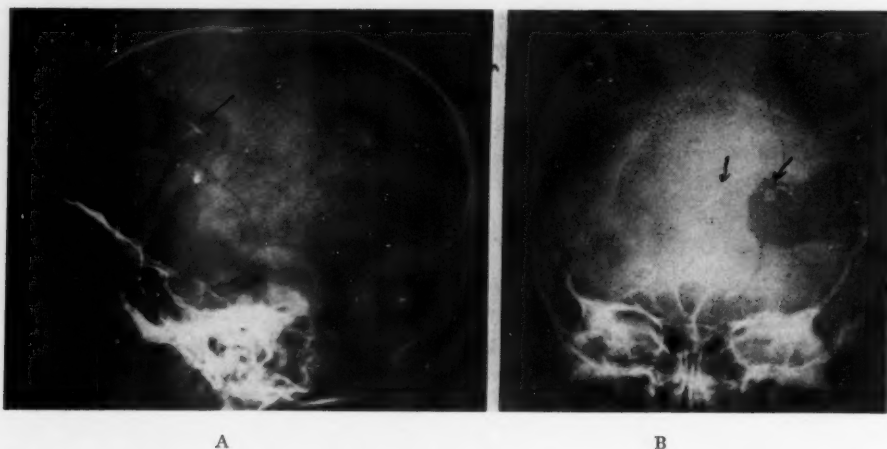


FIG. 6.—Case 14: A and B. Showing large bone defect in right frontal bone, with some deep, retained bone fragments. This patient had had a fascial dural graft three days after injury, followed by infection and development of cerebral hernia.

closed with temporal fascial graft; local sulfanilamide; closure in layers. He was removed to a General Hospital on August 16, where it was noted that the right frontoparietal wound was broken down and exuding pus. The patient was sent to a Station Hospital on August 22, and subsequently arrived here on August 29. Examination showed a dirty semilunar wound, right frontal, with granulations and pus extruding. There was left facial weakness. The right optic disk was blurred and there was cervical rigidity. Roentgenograms here showed multiple linear fractures with a 6 x 2.5 cm. defect of the right frontal bone. Bone fragments were visualized in the brain as well as some metallic fragments at the posterior aspect of the defect, just within the inner table (Fig. 6). On August 30, operation was performed. The semilunar incision, through which projected three small cerebral fungi was reopened, exposing bulging infected brain and a large piece of necrotic fascia, partially attached by multiple silk sutures. The sloughing fascia was removed together with the sutures. There were three separate points draining pus. The bulging mass of infected brain was excised with the electrocautery, exposing in the course of excision several small pockets of pus which were evacuated. Several pieces of bone were found and removed. The underlying brain was necrotic and obviously the seat of spreading infection; this was sucked out. The wound was packed open with a Mickulicz drain. He was placed on a course of sulfadiazine immediately.

Following operation, meningeal signs promptly disappeared, and the optic disks, previously blurred, became clear. The exposed brain began to granulate over, and the

CRANIOCEREBRAL WAR WOUNDS

skin flap became firmly attached except at the lateral margins. On one occasion it was felt that there was a communication with the ventricle which sealed over. A small point of drainage persisted. This was injected with diodrast and was found to extend down for about 2 cm., and there was evidence of osteomyelitis at the lateral bone edge. On October 15, the skin flap was reflected back, and osteomyelitic bone was rongeuired away. The wound was again packed open. Sulfadiazine was given by mouth. The exposed brain became epithelized promptly and the defect was covered with solid epithelium except for a tiny area in the center which was almost healed when the patient was evacuated on November 20.

Case 15.—Age 31, was struck by mine fragments on August 3, 1943. At a Clearing Station that evening, a diagnosis of compound fracture of the left frontal bone, with herniation of the frontal lobe, was made. At operation, the defect was smoothed, hemorrhage controlled, and devitalized brain removed with bone fragments. The wound was packed with sulfanilamide and vaselined gauze. He went through a Field Hospital the next day and reached an Evacuation Hospital on August 5, when reoperation was undertaken. According to the accompanying notes a cerebral fungus was resected, requiring "left frontal lobectomy"; a large foreign body was removed. Sulfanilamide powder was placed in the wound. The dura was closed with a fascial graft from fascia lata. Sliding graft was necessary for scalp closure. He was placed on sulfadiazine and his condition was noted as satisfactory when he was evacuated on August 10. He reached here through the chain of evacuation on August 15.

There was foul discharge through the original head encasement. Neurologic examination was negative, speech was clear. On removal of the encasement, there was a pulsating puffy defect with foul purulent drainage. Skin sutures were removed, resulting in profuse discharge of pus. On retracting the skin edges there was a 5-cm. bony defect in the center of which lay a loose, sloughing fascial graft. The graft was removed together with silk sutures and the wound was packed open. The cerebral fungus responded well, and in the course of a week began to recede. Skin edges were allowed to epithelize over the periphery of the hernia and it healed completely within six weeks, except for one small area medially, which continued to drain a small amount. Roentgenograms, with diodrast, showed a small invaginated pocket. A tiny piece of retained bone fragment was lifted out and a thin rubber drain was inserted. This resulted in prompt healing. The patient was discharged to the Zone of Interior on October 27, 1943.

The persistent infection which complicated the course in Cases 14 and 15 might have been expected in the presence of retained bone fragments plus the addition of a fascial dural transplant with silk sutures in a contaminated field. They also serve to illustrate the inefficiency of incomplete débridement.

"PACKING" OF HEAD WOUNDS

Cases 11 and 15 were both subjected at first to incomplete débridement with sulfanilamide-vaselined gauze packing. We do not believe that this type of dressing is applicable to head injuries. Just as its abuse has been noted in cases of wounds of the extremities, where tight packing results in damming up of infected tissues, the packing of a penetrating head wound with vaselined gauze (if allowed to remain for long) is equally hazardous, particularly when bone fragments and foreign material have not been removed. The following case illustrates this point.

Case 16.—Age 35, received a gunshot wound of the head on February 16, 1943. On the night of the injury he was treated at a Surgical Hospital, where the "scalp wound (was) excised; fracture of skull present; depressed fragments removed; sulfanilamide-vaselined gauze; scalp sutured loosely." He was started on a course of sulfadiazine. The patient arrived here on February 24, 1943. He was confused and irrational. There was

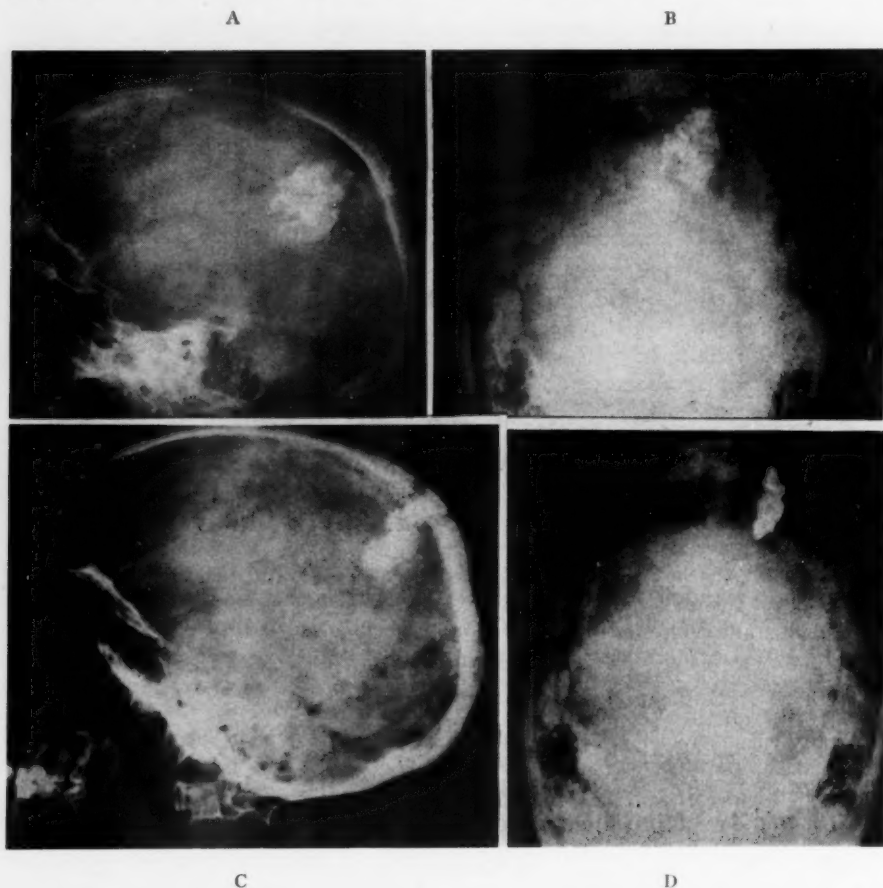


FIG. 7.—Case 16: A and B. Showing extent of abscess as outlined by radiopaque iodoform gauze drain. C and D. Comparable views, taken two weeks later; the abscess cavity has become much smaller and healing is progressing. This patient had retained bone fragments within the abscess cavity; original wound treated with vaselined pack.

early papilledema. The left shoulder girdle muscles were weak and there was drifting of the outstretched left arm. Neurologic examination was otherwise negative. The edges of the infected right parietal scalp wound were held by two silk sutures, which forcibly restrained a vaselined pack. On removal of the sutures, the pack delivered itself, and the underlying wound showed an obvious central defect through which necrotic brain oozed. Roentgenograms showed a depressed comminuted fracture of the right parietal bone with indriven bone fragments. On February 26, operation was performed. After removal of redundant brain tissue, at a depth of 1 cm. a large abscess containing 40 cc. of thick creamy pus was found and evacuated. The abscess wall was moderately thick. Several pieces of bone were found and removed from the cavity. Iodoform drains were placed in the abscess and the skin left open. Roentgenograms, with iodoform drains in place, were taken at weekly intervals, and we were

able to follow the healing process visually (Fig. 7). There was complete healing of the abscess and the skin on April 2. Neurologic examination showed almost no drifting of the left arm and only slight instability on finger-nose test. He was able to walk well. Optic nerve heads cleared promptly. He was evacuated to the Zone of Interior on April 8, 1943.

METALLIC FOREIGN BODIES

The problem of removal of metallic foreign bodies is a difficult one at times. These materials are usually not a nidus of infection, whereas retained bone fragments appear to be responsible for infection in most cases. The occurrence of an abscess around the indriven piece of metal in Case 12 demonstrates that this cannot be considered a hard and fast rule. The following case is cited to illustrate failure on our part to recognize the presence of a large lesion resulting from multiple metallic foreign bodies.

Case 17.—Age 21, was struck by enemy fire on July 12, 1943. The exact type of missile was not known. Operation aboard ship was performed within 12 hours, consisting of débridement, local sulfanilamide and closure of the left temporal wound. The patient was stuporous and had partial paralysis of the left face and leg, at least until July 16, when he reached a Station Hospital. There the temporal wound was found to be infected, and on July 22, a second débridement was done, with drainage. The patient's condition improved and he was evacuated, reaching here on August 8, 1943.

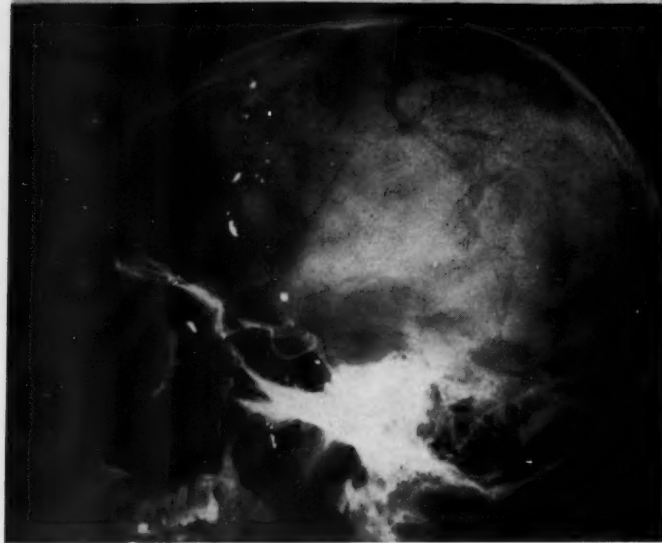
Examination showed an infected left temporal wound with a large amount of drainage. There was swelling below the mandible with trismus. Neurologic examination was entirely negative. Speech was clear. The partial left facial and leg palsy had apparently cleared up while *en route*. Roentgenograms showed a 2.5 cm. defect in the squamous portion of the left temporal bone, with two large metallic fragments at the fracture site; there were several smaller fragments intracranially beneath the coronal suture (Fig. 8 A).

During the next few days trismus became more marked. On August 12 an aneurysm of the internal maxillary artery was found and excised, resulting in relief of trismus. The left temporal wound continued to drain profusely. Neurologic examination remained negative, with normal fundi. Sulfadiazine was given right along, with maintenance of high blood concentration. It was thought that persistent drainage was due to retained foreign bodies at the fracture site.

On August 20, operation was done. The temporal wound was excised down to the anterior part of the pars squamosa. A sinus tract ran down to the bone defect. Lying in the defect were several loose bits of bone, and buried in the zygoma were several pieces of metal, dirt, and hair. All this was removed and the bone edges were rongueured down to healthy bone. The dura was covered over with tough scar and there was no evidence of a tract through the dura, at this time. The wound was closed loosely around a Penrose drain.

Sulfadiazine was continued postoperatively. The wound continued to drain. Postoperative roentgenograms (Fig. 8 B) showed a clean temporal defect, with the previously noted small metallic fragments along the vertex. Neurologic examination was consistently negative. Eye grounds were checked repeatedly by us as well as by the ophthalmologist, and disks remained flat and clearly outlined. Visual fields were full. The patient was mentally clear. Vital signs were normal. He was allowed to get up. On September 17, he complained of general malaise and had low grade fever; neurologic examination was negative. Malaria was suspected, but no parasites were found on smear. On September 18, there was fully-developed meningitis, with temperature 104° F., rapid pulse, and stiff neck. The patient became very confused. Spinal

A



B

FIG. 8.—Case 17: A. Lateral view showing several large metallic foreign bodies (arrows) within a ragged frontotemporal defect. Numerous small foreign bodies scattered throughout the frontal lobe. B. After removal of the large metallic foreign bodies and pieces of bone in the defect. This patient developed an extensive brain abscess which was not recognized clinically.

puncture was done, pressure was 220 Mm. of water. The fluid was turbid, contained 14,000 cells per cc., of which 90 per cent were polys. No organisms were found on smear. Sulfadiazine was continued. On the morning of September 19, temperature was 99° F.; neurologic findings unchanged. At noon he suddenly lost consciousness and died of respiratory failure.

Autopsy showed a narrow tract running through the scarred dura to the temporal lobe. There was diffuse basilar meningitis. The entire left hemisphere felt soft and the gyri in the frontotemporal region were flat and yellow. On section of the brain, a large, thin-walled abscess was found which involved the frontal and temporal lobes, and extended back to the posterior horn of the left lateral ventricle, at which point it had ruptured into the ventricle.

On reviewing this case, there are several significant features. There had been two débridements before evacuation to a General Hospital. After reaching this hospital, despite the large size of the abscess, there were neither general pressure, nor localizing signs. As a matter of fact, mental and emotional instability noted on admission here had disappeared, as had the facial and lower extremity palsy which had been observed aboard the Hospital Ship. From the extent of the lesion demonstrated at autopsy, one would have expected aphasia (the patient was right-handed), visual field defect, and at least partial hemiplegia. The infection had evidently progressed with only thin walling-off despite continued sulfadiazine therapy. For our part, we were led astray by the fact that there was no demonstrable tract leading through the scarred dura at the time of exploration of the temporal wound, as well as by the prevailing opinion (which we share) that intracerebral metallic foreign bodies are not often associated with abscess. In our own experience, indriven bone fragments have most frequently been found in association with infection. The persistent discharge of pus led us to suspect, erroneously, that there might be osteomyelitis of the superior margin of the zygoma. In retrospect, despite lack of general pressure and localizing signs, the mistake we made was in not exploring intradurally with a needle. If it was felt unwise to insert a needle through the infected temporal defect, this procedure could have been done safely through a perforator opening in a clean field.

We believe that the removal of indriven bone fragments, with particles of clothing, hair, *etc.*, is of paramount importance in all cases. If a metallic foreign body is readily accessible and if its removal does not mean inflicting severe functional damage, then every effort made to effect its removal is justifiable. We do not yet know what incidence of traumatic epilepsy may be expected to occur in this war, in head wounds with retained foreign body and cortical scar. In Case 7, it was believed that removal of the foreign body (Fig. 4) which lay near the surface of the left frontal lobe was indicated at the same time that we performed delayed débridement of the right frontal lobe.

Due to the relatively short period in which wounded men remain in the Theater of Operations, we could not expect to encounter many cases of traumatic epilepsy. The following case of jacksonian seizures which came

under our care is cited as our single experience with the condition in this Theater.

Case 18.—Age 24, was struck by high explosive fragment during an air raid on June 6, 1943. He did not lose consciousness. At a General Hospital (British) two hours after injury, examination showed a small penetrating wound of the right parietal region just above the ear. He had a right peripheral facial weakness, partial flaccid paralysis of the left arm, and absent knee-jerks. Débridement, with primary suture, was performed immediately. The immediate postoperative course was uneventful, and he was transferred to a Station Hospital on June 23. The following day he had a jacksonian fit, beginning in the left hand and arm, spreading to the left leg, and then

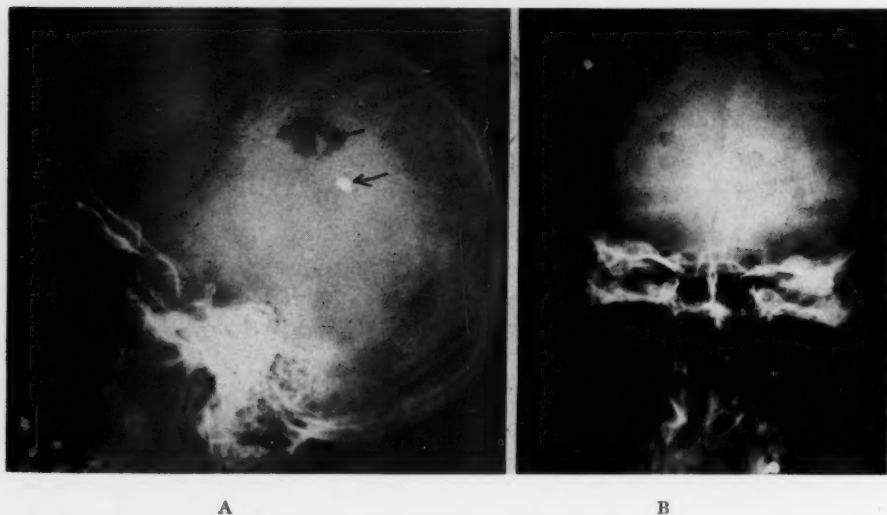


FIG. 9.—Case 18: A and B. Penetrating wound of right parietal bone with retained bone fragment and metallic foreign body. Patient had jacksonian seizures beginning in the left hand. At operation cortical scar with retained foreign body removed *en masse*.

becoming generalized. He was transferred to a General Hospital on June 25, where the wound broke open and drained a small amount of serous fluid. This healed within a few days, and the patient reached this hospital on July 21. There was a healed incision 3 cm. long in the right parietal region, with a small underlying bone defect. The only neurologic abnormalities were astereognosis, ataxia, and lack of fine movements of the left hand. Roentgenograms showed a few loose fragments of bone directly beneath the bone defect and a small metallic foreign body, 1×0.5 cm. apparently within the cortex (Fig. 9). The patient was right-handed.

On July 29, 1943, approximately seven weeks after injury, and one month after the wound was healed, a right parietal craniotomy was done. Through a small bone flap, the original laceration of the dura was found to be covered with tough fibrous tissue which led down through a dense scar to underlying brain. This part of the dural flap was cut out. In the position of the arm area the cortex was yellow and scarred, with the rolandic vein running along the surface. It was possible to peel this vessel away from the lesion and preserve its continuity. Superficial vessels were clipped and cut, and the entire scar with its retained foreign body was removed *en masse*. The defect was 3 cm. in diameter and 2.5 cm. deep. The wound was closed in layers with silk, using a piece of temporal fascia to close the dural defect. While undergoing anesthesia (pentothal sodium), the patient had tonic-clonic movements of the left arm and leg, but did not go on to general convulsion. On two occasions coagulation of

small vessels at the periphery of the cicatrix resulted in flexion of the left hand and arm, and rotation of the shoulder.

On the night of operation, the patient was started on luminal, grains one, three times daily. There was paresis of the left arm and face; the leg was not affected. On the first day, he was able to extend and rotate the arm and hand, and the facial weakness was disappearing. Sutures were removed on the second day, at which time there was no longer any facial weakness, and the arm was improved. The wound healed *per primam*. By the tenth postoperative day arm movements had returned and he was able to manipulate a match box with his left hand as well as before operation. He was allowed up on the 10th day, and his course continued satisfactory. Astereognosis and impairment of fine movements of the left hand were still present when the patient was returned to the Zone of Interior on September 6, 1943. In a letter dated November 1, his sole complaint was sensory impairment of the hand.

In cases in which the retained metallic foreign body is inaccessible, where it is situated in a vital area, the offending fragments should not be disturbed unless it gives rise to abscess later on. Figure 10 shows a metallic fragment

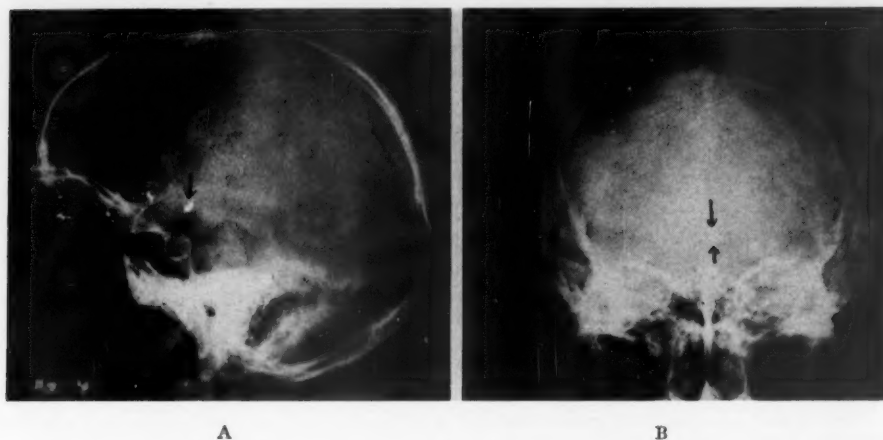


FIG. 10.—A and B. Films of a soldier with a healed penetrating wound of the right orbit. Several retained metallic foreign bodies the largest of which lies in the midline directly above the sella turcica. There had been transient polyuria and polydipsia which cleared rapidly. No attempt at removal of foreign body indicated.

which entered the right orbit of a soldier on February 27th and lodged over the sella turcica. There had been transient polydipsia and polyuria early, but neurologic examination was entirely negative, and there were no hypothalamic signs or symptoms on arrival here on March 8, 1943. Any attempt at removal of the foreign body would have been disastrous.

The following case demonstrates a problem that may arise from time to time:

Case 19.—Age 22, sustained a penetrating wound of the parieto-occipital region on March 28, 1943. There was almost total blindness immediately. On March 31, débridement was performed at an Evacuation Hospital, with removal of bone and metallic fragments from both calcarine areas, "some fragments were inaccessible." At a Station Hospital papilledema was noted on April 10, 1943. He reached here on April 12, 1943. There was a transverse occipitoparietal wound just above the region of the torcula, which was healed except for one area in the center at which point galea was not epithelized.

There was bilateral papilledema. Visual acuity, bilateral, was limited to finger movements at five feet. Roentgenograms showed a defect over the midline posteriorly; there were several metallic foreign bodies including one which appeared to be within the region of the sinus (Fig. 11). We believed, with the original surgeon, that removal of the fragments should not be attempted unless absolutely necessary. Aspiration with a needle through intact lateral margin of the defect yielded a few drops of sero-sanguineous fluid; no pus. The eye grounds were checked repeatedly, and papilledema receded gradually, so that there was no measurable elevation by April 24. Visual acuity rose to 3/200 in each eye. Tangent screen examination on May 11, showed right homonymous central field defect with involvement of the maculae. The unhealed portion of the wound healed within a few days. The patient was able to be up and about and was discharged to the Zone of Interior on May 16, 1943. Had signs of pressure persisted, we would have been obliged to remove the shell fragments as a source of infection.



FIG. 11.—Case 19: A and B. Wound of occipital region, midline, with retained metallic foreign bodies just above the torcular Herophili. Admitted after early incomplete débridement, with choked disks. Under conservative treatment, pressure signs disappeared, and there were no signs of abscess. Foreign bodies were not removed.

Parenthetically, it might be added that an attempted removal of these foreign bodies in the forward echelon, without adequate facilities would have courted disaster.

[CLOSURE OF] WOUNDS

In early cases, following débridement, it has been an accepted neurosurgical practice to close the head wound tightly, without drainage. Such closure after careful toilet of the wound will almost inevitably result in primary healing, and will prevent the development of a cerebral hernia, with its long period of morbidity. At times, there has been so much loss of skin that after excision of only a narrow margin, difficulty in closure is encountered. If undermining does not result in sufficient mobilization of the scalp, one may then be forced to use releasing incisions and "sliding grafts." If this procedure is performed, sufficient relaxation must be sought to allow closure without too much tension, and the releasing incisions must be so placed as not to jeopardize the vitality of the primary wound.

We have had to resort to releasing incision in only one case, and in that

instance (Case 8) it is worth pointing out that one part, however small, of the primary wound was not fully healed until the 12th day; this was due to too much tension. The following case is presented as an instance in which laterally placed releasing incisions appeared to have jeopardized the vitality of the central wound, although local infection was probably the main factor.

Case 20.—Age 49, was hit by shell fragments on April 23, 1943, sustaining a penetrating wound of the vertex. He was taken to an Evacuation Hospital, where pre-operative examination noted "neurological essentially normal, except for semicoma." Roentgenograms showed a defect in the vertex of the skull, with a metal fragment deep in the right temporal lobe. The wound was débrided on the day of injury, exact time interval not known. The superior sagittal sinus, which ran through the wound was successfully avoided. Bone fragments were removed, but the metallic fragment was not looked for. The dura was not closed. To close the scalp, two lateral releasing incisions were made. The patient was transferred to another Evacuation Hospital on April 25, where "sensory epilepsy" was noted. At a Station Hospital on April 30, paralysis of both legs was observed. The patient arrived here on May 4, 1943.

Examination showed an area about 6 cm. in diameter directly over the vertex, which was red, hot, and swollen. There was a central tripod incision, flanked by two lateral releasing incisions, about three inches long. The three wounds were covered with pus, and the tripod had broken down, with cerebral fungus protruding. From the relative position of the anterior limbs of the tripod and the releasing incisions, it was thought that blood supply to the central wound was not adequate. The patient had terrific paroxysmal pain in both legs. The left leg was completely paralyzed; the right partially so. Both disks were blurred. The right pupil was larger than the left. There was marked incoordination and loss of fine movements in both arms, particularly the left. There were no pathologic toe signs. Sensation was definitely diminished and position sense was absent in both legs.

The head was shaved and wet dressings were applied for a few days to reduce the cellulitis. Fluid intake was limited, although sulfadiazine was given. After cellulitis had disappeared, aspiration with a needle through a clean field was done to rule out possible abscess; no pus was obtained. The bulging hernia was then treated with boric-vaselined dressings. Lumbar puncture was done twice to reduce the protruding mass. After subsidence of the cellulitis and infection, the hernia receded and epithelization began. *Pari passu* with recession of the hernia the patient's condition steadily improved. On June 6, 1943, there was complete healing of the tripod as well as the releasing incisions, and the defect was flat. Disks were normal. The patient was free of pain. Abnormal signs in the upper extremities disappeared. He was able to move all muscle groups of the lower extremities, but was not yet able to support his own weight. There was marked ataxia on heel-knee test. Absent position sense below hips, and loss of fine discriminatory sensation below the costal margin. There was no clonus or pathologic toe signs. The patient was discharged to the Zone of Interior on June 15, 1943.

In late cases, closure may be attempted if there is no massive infection, and if removal of all involved necrotic tissue and retained fragments is accomplished. This has been carried out successfully in cases cited previously. Although it was also successful in Case 12, in the presence of abscess, we realize that this was a risky procedure, and this case would have been more safely handled if drainage had been instituted.

HERNIAE CEREBRI

In a certain number of cases, cerebral hernia is bound to occur. In our series, this complication was noted in either (1) cases incompletely débrided and closed, and broken down by infection; or (2) cases which were so badly infected by the time first medical treatment was available that closure was deemed unwise; or (3) cases which were débrided but were not closed tightly.

Treatment of such herniae is conservative. If superficial infection is taken care of, recession of the hernia with epithelization usually occurs, unless there are retained bone fragments or other material which act as a focus of deep infection. In cases without retained material, we have dressed these wounds with fine mesh, vaseline- or boric ointment-impregnated gauze, after preliminary cleansing with boric acid solution or wet saline dressings. If the hernia is large, lumbar puncture is done to promote recession of the mass. Where bone fragments are retained beneath the surface, there will usually be a draining sinus through the hernia, and prompt removal of the fragments, with drainage, will save time and may prevent more serious complications. If the hernia continues to enlarge and shows no signs of recession, underlying brain abscess should be suspected, and if this is present, should be treated by uncapping the hernia and instituting drainage. It is our opinion that drainage, with removal of contained bone fragments and foreign bodies in the abscess, should be performed promptly.

The following case represents an unhappy outcome due to abscesses beneath a cerebral fungus:

Case 21.—Age 24, prisoner of war, sustained a penetrating gunshot wound of the left frontoparietal region on May 5, 1943. Available records began only after his first admission to an American Evacuation Hospital on May 11. At that time, he was aphasic and had right hemiplegia; pulse was slow; the left pupil was larger than the right. The previously sutured scalp wound was infected. Roentgenograms revealed a slight shift of the calcified pineal body to the right and downward. On May 12, the infected scalp wound was opened, with escape of pus and blood. The brain was apparently sealed over and was not disturbed. The wound was left open, with sulfanilamide and vaselined gauze. A left subtemporal decompression was then done. The patient was transferred here on May 20, 1943. Examination showed tense, subtemporal decompression. Near the vertex on the left, there was a cerebral hernia which bulged moderately. There was aphasia and right hemiplegia. On May 26, 1943, operation was performed. The edges of the old infected cruciate wound of the vertex were retracted. Redundant hernia was excised, and at depth of 4 cm., a large multiloculated left frontal lobe abscess, with retained bone fragments, was evacuated and drained with iodoform gauze. Immediately following the procedure, the subtemporal decompression became flat and remained so for a week. With iodoform drains in place, roentgenograms demonstrated apparent healing of the large abscess. Another abscess was suspected in the inferior part of the frontal lobe in the vicinity of a retained metallic foreign body. This proved to be a small one when aspirated through a perforator opening on June 8. The patient received continuous sulfadiazine therapy from May 26 until he died on June 22. Autopsy revealed complete healing of the large multiloculated abscess which was drained on May 26. Throughout the remainder of the left hemisphere, including

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the occipital lobe, however, there were multiple small abscesses, with a small amount of pus in the left lateral and the third ventricles.

SUMMARY AND CONCLUSIONS

(1) The experiences in the treatment of craniocerebral wounds in a General Hospital in the North African Theater of Operations are presented.

(2) Early complete débridement of head wounds, with anatomic closure in layers, and without drainage, is the most desirable type of therapy.

(3) Satisfactory results may be achieved by thorough débridement, even when there has been a very long delay. In selected cases, delayed débridement, with tight closure, and without drainage, has been successful after as long as 32 days. The establishment of any arbitrary time limit within which definitive treatment may be given is not indicated.

(4) If facilities for definitive neurosurgical therapy are not available in the forward echelons, it is to the patient's advantage that he be transported to an area where such facilities are available, rather than be subjected to inadequate early treatment. Prior to evacuation, the scalp should be shaved and a sterile dry dressing, with sulfonamide crystals, applied.

(5) Facial transplant for repair of dural defects is hazardous in late cases.

(6) "Packing" with sulfanilamide-vaselined gauze is not applicable to the treatment of craniocerebral wounds.

(7) Retained bone fragments, with or without foreign materials, are the most common source of persistent suppuration, and their removal is almost mandatory. Metallic foreign bodies do not commonly act as a focus of infection, but may do so.

(8) Sulfonamides have been used in the treatment of this group of cases. However, as a rule, we have not used sulfonamides locally, but have given these drugs parenterally and orally.

SECONDARY SUTURE OF WAR WOUNDS

A CLINICAL STUDY OF 305 SECONDARY CLOSURES

LIEUT. COL. HARWELL WILSON, M.C., A.U.S.

DELAYED WOUND CLOSURE in civilian practice is a procedure which is not frequently employed. In the care of battle casualties, secondary closure of the wound plays a vital part in the early return of soldiers to duty. Experiences gained during the past year have reemphasized certain surgical principles involved in the management of these wounds. It is believed that the principles involved in the successful management of war wounds are equally applicable to certain traumatic wounds seen in civil practice.

Adequate débridement without suture of war wounds in the initial stage of treatment is a necessary principle, the importance of which has been repeatedly emphasized.¹ This procedure is necessary because of the extensive devitalization of tissue so frequently found in war wounds, the extensive contamination of such wounds with foreign material, and the time-interval often present between receipt of the injury and the initial surgical treatment. During a period of rapid evacuation of war casualties, it is often necessary for an individual to be cared for by a number of different surgeons within a relatively short period of time. This fact, alone, would make primary closure a dangerous procedure except in some special cases such as some wounds involving the head, face or chest.

Due to the necessity of extensive débridement without suture, many war wounds require a long period of time for healing to occur unless secondary closure is performed. From the military point of view it is important to secure early healing in order to return the soldier to duty as soon as possible. For the individual, successful secondary closure usually means a better functional and cosmetic result, a more rapid improvement in general condition due to the closure of an open wound, and the avoidance of the possibility of long-protracted ulceration in a large cicatrix. Ulceration may result from lack of blood supply to the central area of such a cicatrix left to heal by second intention.

In a preliminary communication we reported in detail our experience with a group of 138 secondary closures.² Since this report was written our experience has been more extensive with cases of this type, and we have also had an opportunity of seeing more cases relatively soon after the receipt of the initial injury. Overseas military hospitals are employing delayed closure successfully on a very extensive scale, as shown by the recent reports of Kirtley and Trabue,³ Rusbridge, Krajeski and Silver,⁴ and others.

Types of Wounds Suitable for Secondary Closure.—The wounds most suitable for this procedure are those involving soft tissues which have been

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adequately débrided within the past ten days, that have not been subjected to frequent changes of dressing, and which appear clinically to be relatively clean. Wounds older than ten days showing slight infection in patients who are fever-free may be prepared for closure by a short period of warm wet dressings. Studies are now being undertaken in certain specially designated installations to determine whether or not successful secondary suture may not be accomplished in certain compound fractures. It is also hoped that with careful use and good judgment, penicillin may extend the use of delayed closure to some other cases where at present it is not believed to be a desirable procedure.

Factors Favoring Successful Secondary Wound Closure.—These factors are essentially the same as those of importance in the healing of any wound by first intention. Of greatest importance is a wound which is relatively free from infection. Closure without tension, adequate hemostasis, the avoidance of dead space, and suitable postoperative splinting are the most important local factors favoring successful secondary closure. Attention to systemic factors favoring wound healing are important in these cases because many of the patients may be suffering from anemia as the result of extensive blood loss at the time of injury, the diet may not have been adequate during a prolonged period of combat, and the patient is likely to be greatly fatigued.

A normal red cell count, hemoglobin, plasma protein, and vitamin C level in the blood are all especially important in the proper management of such cases.^{5, 6, 7, 8, 9, 10, 11}

Sulfonamides have been employed systemically and locally in some cases. It is fair to state, however, that successful closures are possible in a high percentage of cases without the use of these drugs. In our experience, it seemed that wounds clean enough to close would almost always undergo primary healing without sulfonamides. Whereas, if they appeared insufficiently clean for suture, sulfonamide would not enable a closure to be successfully accomplished. This agrees with the findings reported by Kirtley and Trabue.³

Preparation of Wound for Closure.—Wounds considered applicable for possible closure were carefully guarded from contamination. They were usually inspected briefly, using mask and instrument technic. The final layer of vaselined gauze covering the wound was usually left in place until the patient was actually in the operating room. Extensive wounds were usually dressed in the operating room. In some cases which did not appear to be clean, a period of warm, wet pressure dressings was used from two to five days prior to suture.

Method of Closure.—Experience showed that the optimum method of wound closure varied to some extent with the type of wound. In cases having had an adequate débridement within the previous five to seven days, that are fever-free, and at the first dressing appear to be clean, the method of choice is a simple closure consisting of interrupted sutures either plain or of the vertical mattress variety. Wounds older than ten days usually require a period of wet dressings, and do best when treated in a different manner. Such

wounds are much less pliable, the tissues having become relatively fixed. These wounds are best closed by total or partial excision of the wound. In such instances it is best to remove approximately $\frac{1}{8}$ - to $\frac{1}{4}$ -inch of skin and subcutaneous tissue. The granulating base is also best excised. In our earlier experience it was felt that such treatment in old wounds might break down natural barriers to infection. It is believed that the complete obliteration of dead space accomplished by wound excision in the older cases is an important factor in producing primary union in such cases.

ANALYSIS OF CASES

This report deals with a group of 305 secondary closures performed upon 209 patients. The interval from the time of débridement to the time of closure varied from 4 to 47 days. The size of the wound varied from that of a few centimeters to one wound measuring 30 x 8 x 4 centimeters. The majority of the wounds involved the extremities; however, secondary closures were performed on almost every part of the body.

The time of closure was based upon (a) the time the patient arrived at our hospital from forward installations; and (b) the gross appearance of the wound. In 79 closures, cultures were made prior to operation; however, if the wound appeared to be clean on inspection, operation was usually carried out without further delay. In 73 wounds bacteria were found. In almost every instance the organism grown was the staphylococcus. No streptococci were cultured from these wounds.

Results of Closures.—The best results, as mentioned above, were obtained in cases closed within ten days of the primary débridement. Five to seven days would be considered the optimum time. There were 224 closures performed within ten days of the initial débridement. One hundred-ninety closures, or 85 per cent, healed without evidence of infection. In 25 cases, or 11 per cent, there was slight infection necessitating the removal of one or two sutures. It is pointed out that in these cases, however, much time was saved for the patient. In only nine instances, or 4 per cent, of this group, did total breakdown of the wound occur. Thus, all of these closures except the 4 per cent that completely broke down may be said to have been of benefit to the patient.

Among the closures undertaken after a period of ten days, 37 wounds were closed by simple suture, undermining the edges of the wound slightly if necessary for closure without tension.

Thirty-eight per cent healed absolutely *per primam*, in 54 per cent it was necessary to remove one to three sutures because of slight infection, while 8 per cent showed total break down of the wound, and were listed as failures. In 44 cases beyond the ten-day interval that were treated by excision of the wound and suture, 64 per cent healed absolutely *per primam*, in 32 per cent it was necessary to remove from one to four sutures, and in only 4 per cent of the closures did the wound completely break down. In a few of the cases a rubber tissue drain was placed in the wound at the time of closure. As our

SECONDARY SUTURES OF WOUNDS

experience increased fewer wounds were drained and the results seemed to be improved. In wounds involving deep fascia or muscle depths, or in old wounds that previously had shown the presence of an extensive infection, a rubber tissue drain is still felt to act as a safety valve and, if removed at the proper time, causes little trouble. Drains, however, should by no means be used as a routine procedure if primary healing is expected in a high percentage of cases.

Seventy-nine wounds were cultured preoperatively and organisms were grown, usually staphylococci, from 73 wounds. No streptococci were found. It is our feeling that practically all of the wounds contained some bacteria and that only a quantitative difference existed. From a practical standpoint, cultures were of relatively little aid, as the clinical appearance of the wound offered sufficient criteria upon which to base closure of the wound.

Concomitant Secondary Closure and Skin Graft.—In some instances where there has been extensive tissue loss complete closure without tension may prove difficult or impossible. In such instances it was found that complete closure was usually best accomplished by covering the remainder of the wound with a split-skin graft at the time of partial closure by secondary suture. This method was found applicable to both early and late closures. In some cases with extensive loss of tissue, when adequate débridement had been performed and the wound had not been dressed, a large split-graft was applied at the first dressing in the operating room, when the extremities of the wound were partially closed by suture. In some other instances, late cases where warm wet pressure dressings were used to prepare the wound for closure, split-grafts were also successfully used to secure closure without tension.

SUMMARY AND CONCLUSIONS

1. Successful secondary closure of adequately débrided war wounds can be accomplished safely in a high percentage of cases.
2. Closure within a ten-day interval results in a higher percentage of wounds which heal by first intention.
3. In old wounds the best results were obtained by wound excision.
4. Wounds with extensive loss of tissue may often be closed early by the concomitant use of secondary suture and a split-skin graft.
5. The importance of both local and general factors in wound healing is emphasized.
6. The conclusions expressed in this report are based on a study of 305 secondary closures.

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REFRIGERATION ANESTHESIA AND EVALUATION OF AMPUTATION SITES BY ARTERIOGRAM

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PHYSICIANS AND SURGEONS today are becoming more familiar with the work done on cooling or refrigerating living tissues, Frederick Allen,¹ Brooks and Duncan² and Temple Fay,³ and their associates, have made the greatest contributions up to the present time. Allen reported his experiments on the tourniqueted limb immersed in ice about five years ago. He discussed the physiology of the ligated limb with reference to preservation of tissue, lowered metabolic requirements and the surgical possibilities available to us under lowered temperatures, Brooks and Duncan made their studies of the effects of temperature on the survival of anemic tissue. Temple Fay reports 100 cases of general refrigeration where the whole body temperature is reduced to around 80° F. to 90° F.; the lowest temperature obtained was 74° F. by rectum and the longest period of refrigeration was eight days.

This discussion will be limited to the use of lowered temperatures for the purpose of limb amputations. In the Montreal General Hospital the procedure was carried out on 22 patients. The cases referred to were in nearly every instance grave operative risks, some of them would not have been offered the help of surgery if it were not for this method of anesthesia. For example, there is the severely injured who is already in shock, or the diabetic arteriosclerotic, and the cardiorenal deficiency case; then there is the senile decrepit type who through malnutrition or chronic disease would not weather a standard type of operative procedure under general or spinal anesthesia.

FATALITIES

As there are four deaths in this small series it may be instructive to go into some detail with each fatality.

Case 1.—A male, age 56, was brought in by ambulance, suffering from a fractured skull and a compound fracture of the left femur. The soft tissue injury at the site of the fractured femur was extensive and involved tearing of muscle sheaths and mangling of the muscle fibers. For the first three days he was treated for shock, and during this time the injured limb was splinted and a thorough débridement of the wound was carried out, followed by a sulfathiazole emulsion pack. On the fourth day the temperature rose to 103° F. The limb became dark in color, although the popliteal pulsation was still palpable. There was a foul odor from the wound, and the general picture was one of septic absorption. It was felt that a high amputation was the only hope of saving his life. This was undertaken under refrigeration. He died the next day. Postmortem showed *Cl. welchii* in the thigh muscles.

Case 2.—A female, age 80, suffering from arteriosclerosis. She had hypertension, a rough systolic murmur, and the heart grossly enlarged to the left. There was ankle edema and shortness of breath. On the right heel was a dark reddish patch and from

that area was a gangrenous process spreading over the foot. Amputation seven inches below the knee joint was carried out under refrigeration. For some unaccountable reason in this case the ice pack contained salt and the surface temperature was reduced to the freezing point. When the leg was lifted out of the ice in the operating room there were blebs on the skin surface due to the excessive low temperature. These were aspirated and on culturing were shown to contain *Cl. welchii*. She was treated at once by every means in her defense but died of gas gangrene seven days later.

Case 3.—An elderly woman of uncertain age. She also had arteriosclerosis and diabetes with gangrene of the left leg. An ice pack was instituted in the usual way and a mid thigh amputation carried out without any apparent ill effects. She died of a cerebral hemorrhage a few hours after operation.

Case 4.—Female, age 57. An arteriosclerotic diabetic, almost blind. She had been admitted several times previously for an unhealed ulcer on the right heel. On the present occasion, there was evidence of a spreading gangrene over the foot and ankle. The dorsalis pedis artery and the peroneal artery were pulseless. The popliteal artery was, on the other hand, quite normal. An amputation at the site of election was carried out under refrigeration. She died of a rapidly progressing gas infection on the fourth postoperative day.

COMMENT.—Since three of the deaths were due to gas gangrene we have naturally been very disturbed. The first case with the deep muscle wound fell in line very well with our knowledge and experience of gas infections. The second case, however, had no open wound until the blebs were formed by the unfortunate excessive low temperature caused by the salted ice. We then feared that we were introducing the organism through the medium of river ice and henceforward decided to use artificial ice or mechanical refrigeration entirely. The fourth case died of gas gangrene in spite of the precautions prompted by the previous experience and improved technic. The only open wound was a chronic gangrenous ulcer surrounded by inflammatory tissue. There was, however, thick, dark colored leathery skin about the ulcer and covering a tough, ligneous deep tissue surrounding the lymphatics. Gas-forming organisms have been isolated on numerous occasions from devitalized tissue in the region of chronic ulcers. We are of the opinion that the spores may lie dormant in the lymphatics and also in the deep tissues surrounding the lymphatics. It is probable, too, that tissues so affected may extend high up in the limb.

GENERAL PROCEDURES

Refrigeration anesthesia cools and numbs the tissue cells *en masse*. It is, therefore, a general tissue depressant without any particular selective action on nerve trunks. Refrigeration produces first of all a vasoconstriction and later a vasodilatation; this reduces edema and minimizes transudation of tissue fluids rendering the tissues firm. Shortly after refrigeration commences there is a mild analgesia over the once painful extremity. The patient, relieved of his agonizing pain, may now enjoy a substantial meal before going to the operating room or immediately afterward. There is no shock to the procedure whatsoever, as determined by the ordinary signs and symptoms or by the Scudder estimation. There is no real necessity of a sedative although in many nervous people it is probably advisable. The anesthesia is

REFRIGERATION ANESTHESIA

TABLE I

Hosp. No.	Date	Sex	Age	Reason for Amputation	Site	Material used	Drainage	Result
1937	Apr. 11/42	F	56	Diabetic gangrene	6" below knee	C.G. & Dermol	No	Primary healing
2394	Apr. 20/42	M	49	Severe injury	Upper third thigh	C.G. & Dermol	Yes	Died
2909	May 12/42	M	70	Art. scl. gangrene	6" below knee	C.G. & Dermol	No	Primary healing
2150	July 2/42	M	29	Severe injury	Mid calf	Chr. c.g. & s.w.g.	No	Secondary repair
4866	Aug. 26/42	M	75	Art. scl. gangrene	6" below knee	Chr. c.g. & s.w.g.	No	Primary healing
2686	Aug. 27/42	M	64	Lues — gangrene	Mid thigh	Chr. c.g. & s.w.g.	No	Primary healing
5428	Aug. 31/42	F	62	Diab. gangrene	6" below knee	Chr. c.g. & s.w.g.	No	Primary healing
5781	Sept. 21/42	M	26	Ca. right foot	6" below knee	Chr. c.g. & s.w.g.	No	Primary healing
6121	Sept. 30/42	M	61	Diab. gangrene	6" below knee	Catgut & s.w.g.	No	Primary healing
8189	June 6/43	M	38	Severe injury	6" below knee	Catgut & s.w.g.	No	Secondary repair
8283	Feb. 22/43	F	65	Diab. gangrene	Lower third thigh	Silk & Dermol	No	Primary healing
2175	Apr. 15/43	M	38	Severe injury	Lower third forearm	Chr. c.g. & silk	No	Primary healing
2463	June 21/43	F	80	Art. scl. gangrene	6" below knee	Chr. c.g. & silk	No	Died
2801	June 24/43	M	75	Art. scl. & abscess	Amp. hand	Chr. c.g. & silk	Yes	Primary healing
5780	Sept. 20/43	M	77	Art. scl. gangrene	Mid thigh	Chr. c.g. & silk	Yes	Delayed healing
5834	Aug. 21/43	M	65	Embolism popliteal	Mid thigh	Chr. c.g. & silk	Yes	Delayed healing
6458	Oct. 14/43	M	76	Diab. gangrene	Mid thigh	Chr. c.g. & silk	Yes	Died
7134	Nov. 20/43	M	51	Diab. gangrene	6" below knee	Chr. c.g. & silk	Yes	Died
316	Jan. 21/44	F	58	Diab. gangrene	6" below knee	Chr. c.g. & silk	Yes	Delayed healing
856	Mar. 20/44	F	60	Diab. gangrene	6" below knee	Chr. c.g. & silk	No	Delayed healing
391	Mar. 31/44	F	71	Diab. gangrene	Mid thigh	Chr. c.g. & silk	Yes	Primary healing
1543	Apr. 15/44	M	74	Emb. popliteal	Upper third thigh	Chr. c.g. & silk	No	Secondary suture

c.g. = catgut; Chr. c.g. = Chromic catgut; Art. Scl. = Arteriosclerotic.

adequate and will last about one hour, thus allowing the surgeon to carry out any type of amputation procedure he desires. The sawing of the bone sometimes disturbs the patient but he will generally admit there is no pain. Severing of the large nerve trunks is quite painless but one cannot pull the nerve down from a higher cut without some pain; to obviate this discomfort it is quite easy to separate the muscle fibers upwards an inch or so and in that way cut off the nerve above the line of amputation. Or, if the surgeon desires, he may inject novocaine into the nerve, or novocaine and alcohol, to avoid the painful neuroma later. This brings up the question of the tourniquet, and perhaps suggests its only value. In a completely ligated limb the large nerve trunks are absolutely senseless to pain, whereas in the nonligated limb the analgesia is sufficient to handle the nerve without undue discomfort.

TOURNIQUET

Allen, and his coworkers, have proved to their own satisfaction that the tourniquet is harmless under reduced temperatures. Others have remarked that the dangers of the tourniquet are reduced but not entirely eliminated. Gerald Pratt⁴ stated that: "Ice is reserved for those patients whose chances of surviving a general anesthetic are very poor and where the dangers of the tourniquet are less than the dangers of anesthesia." In the small series at the Montreal General Hospital the tourniquet was dispensed with in 18 of the 22 cases. This was done, realizing fully that warm blood was surging through the depth of the limb to be chilled. The only precaution was to chill the limb long enough and high enough, an average of four hours for the upper third of the tibia and five hours for thigh amputations. It is now common knowledge that the limb can be immersed in ice for days, as long as there is no tourniquet. We have attributed the early and uneventful healing of the stump wounds to the fact that the tourniquet was not used in these cases. It must be borne in mind that the tissues dealt with here are already devitalized and the trauma of the scalpel alone may be more than the local healing processes can deal with. The tourniquet, we believe, weighs heavily against early healing by adding further trauma through local pressure on unfavorable tissue material which is traversed by sclerosed capillaries to the wound edges.

TECHNIC OF APPLICATION

The technic used is a modification of that described by Allen. Usually a mild sedative is given before immersion of the limb into the ice. We have used $\frac{1}{6}$ gr. morphine sulfate and $\frac{1}{100}$ gr. hyoscine. The refrigerating apparatus is made up by materials which are available in any ward. First, an ordinary single leg cradle is inverted in the bed and lined with a rubber sheet sufficiently long to extend from the ischial tuberosity downwards to beyond the foot of the bed and into a pail on the floor. Finely chopped artificial ice is then distributed about four inches in depth along the floor of the



FIG. 1

FIG. 2

FIG. 1.—Produced by injecting 20 cc. 70 per cent diodrast into the femoral artery just below the inguinal ligament. Showing patency of femoral artery and popliteal artery, with its bifurcation into the anterior and posterior tibial arteries. Some cases show a very much better geniculate anastomosis.

FIG. 2.—Arteriogram of Case No. 5834. Produced by injecting 15 cc. diodrast into the femoral artery just beneath the inguinal ligament.

Note the absence of continuity of the lower part of the femoral artery and the upper part of the popliteal, with filling of the popliteal through anastomotic network, which, although patent, is insufficient for maintenance of the lower leg.

trough from the ischial tuberosity to beyond the foot of the patient. The limb is then placed upon the four-inch mattress of ice. Sufficient ice is then added to bury completely the member including the toes. The head of the bed is elevated enough to allow adequate drainage of the melting ice down the rubber trough into the pail on the floor. This drainage is important to obtain a constant temperature and prevent maceration of the skin. The ice should be replenished frequently to compensate for melting and settling. The temperature thus obtained at the skin surface is about 5° C. If a tourniquet is to be used it is applied one hour after refrigeration

commences. During refrigeration the patient may be given coffee or whisky or a regular meal. The duration of ice pack with the tourniquet is about two hours for ankle, three hours for the upper tibia, and four hours for thigh amputations. Without the tourniquet the refrigeration required is about one hour more at each site but it may go on indefinitely without harm. When the patient is brought to the operating room the surgeon and his assistant must be scrubbed and prepared to operate. The patient is lifted out of the ice pack and the leg prepared with ether, alcohol and iodine. Note that this is the only skin preparation the limb has been given. The lower part of the extremity is bandaged and the draping completed. It is preferable to use cold saline and cold instruments but the operating room is kept at the regular temperature. The amputation procedure is carried out with leisure, and the wound usually closed without drainage. A compression dressing is applied to the stump and the patient returned to the ward with three ice bags over the dressing. One ice bag is removed every 24 hours.

AMPUTATION SITE

The amputation site is undoubtedly going farther down the limb. This is attributed not only to refrigeration without tourniquet and improved metabolic condition of tissues, but also to the use of arteriograms. Ice anesthesia enables the surgeon to reamputate without undue risk, but if an arteriogram is available and the proper site ascertained it is a sounder procedure. Very often there is a wide and adequate collateral circulation, allowing a low amputation site; on the other hand the surgeon may believe he is feeling a pulse in the popliteal space when actually the impulse is being transmitted through five inches or more of blood clot.

The color plate, consisting of six individual cuts, has been arranged to show the salient features in connection with refrigeration anesthesia, according to the Montreal General Hospital technic, omitting the use of a tourniquet.

The case is one of a diabetic, who had been bedridden for three to four years on account of recurrent ulceration and cellulitis of the right foot; ultimately rendering the lower leg and foot a constant source of infection, pain and irritant to the diabetic condition.

The lower leg and foot shows deformity, blanching and pigmentation, before emersion in the ice pack (Fig. 1).

The cradle is improvised as a structural support for a rubber sheet, forming a trough, which extends approximately to the ischial tuberosity and distally is extended as a spout for drainage into a pail. Four inches of finely chopped ice (snow) is placed at the bottom of the trough, the limb is then placed on the bed of ice and entirely covered with ice, including the great toe. A thermometer is placed in the ice and the head of the bed is elevated about one foot to give adequate drainage. As you will see, the patient appears comfortable and rested (Fig. 2).

After a minimum period of four and one half to five hours, the patient is wheeled to the operating room on her bed, with ice pack *in situ*. The lower end of the trough is opened by relaxing the paper clips and the ice is disposed of by emptying into a pail (Fig. 3).

The patient is rapidly transferred from the bed to the operating table. The limb is dried with a sterile towel. You will notice that the lower leg shows a very definite erythema when compared with Figure 1; a typical finding when satisfactory refrigeration anesthesia has been attained. The limb is then rapidly prepared with ether, alcohol, and iodine. This, incidentally, is the first skin preparation and the only one. We do not shave (Fig. 4).

The limb is draped with all the staff on hand. The amputation is carried out in the routine manner according to classical amputations. There is no need to hurry; as the skin is divided it retracts very little. The tissues are firm and easily handled. The muscles retract slightly, do not twitch, and are easily cut, and the bleeding is minimum. On sawing the bone, some of the patients have a sensation as if having a tooth drilled. There is no pain on ligation of the vessels. Injection of novocaine and alcohol prior to division of the nerve is advisable but not necessary (Fig. 5).

Bleeding points are ligated with 'C' silk. The vessels ligated with No. 2 silk. The wound is closed without drainage, utilizing subcutaneous sutures with 'C' silk, and skin apposition with vertical mattress sutures of No. 2 silk (Fig. 6).

Upon completion of amputation, a pressure dressing is applied, consisting first of gauze, then absorbent, held in position by a gauze bandage which has been soaked in water. The gauze bandage when soaked, dries and shrinks, giving adequate pressure. This is reinforced by a sterile plumber's waste dressing, held in position by a flannel bandage. No attempt is made to use any other form of splinting. These dressings are not disturbed for a period of ten days unless there is a smell of stale urine, which is, in our opinion, the first indication of gas infection.



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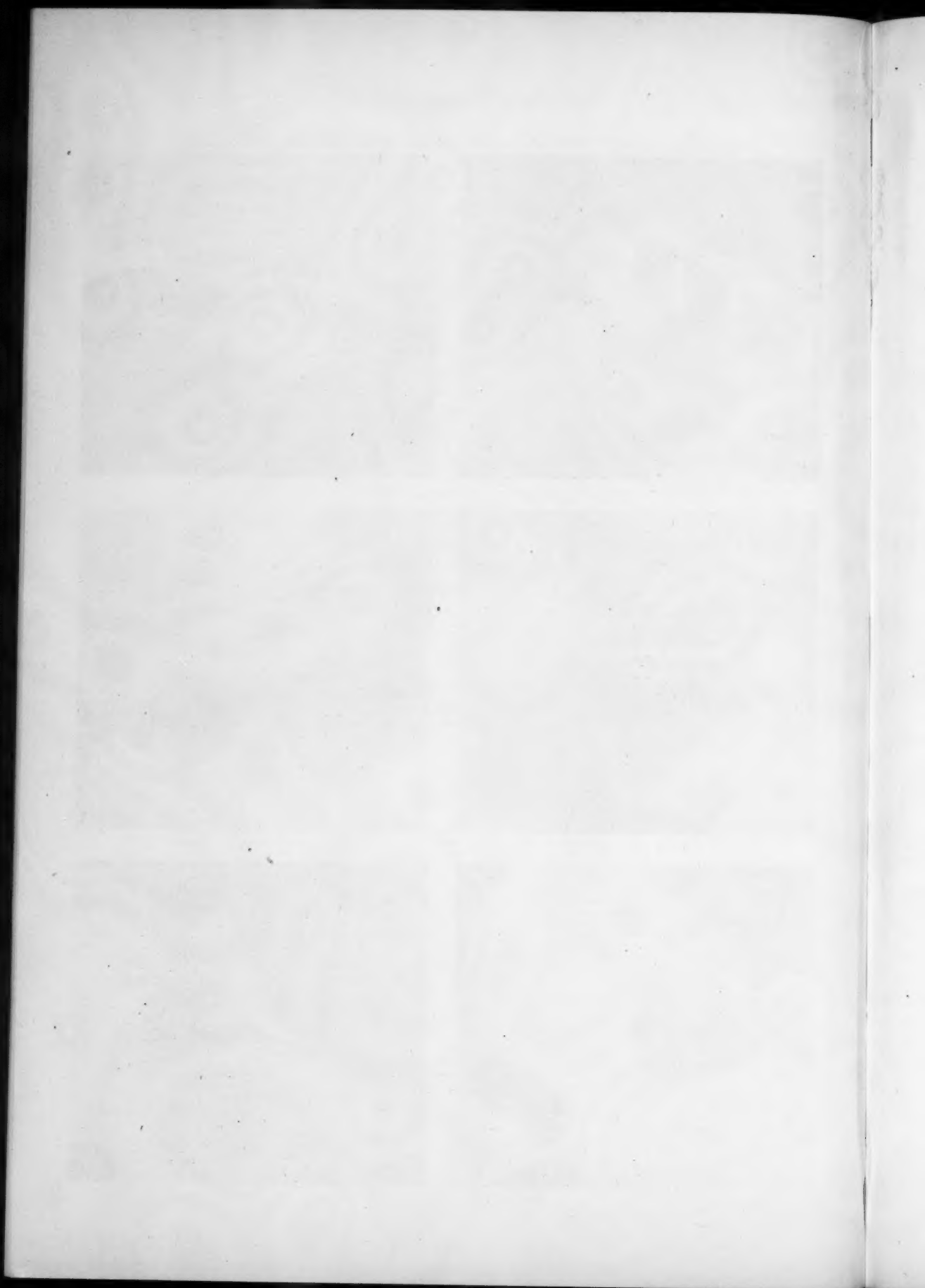
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Arteriography is a comparatively new field but will undoubtedly offer a great contribution in establishing for us the proper site for amputation and go hand in hand with refrigeration in the conservation of limb length and lives. Our experimental work in arteriography has rendered us many interesting determinations with regard to the collateral circulation which we have been unable to ascertain by skin temperatures or oscillometric readings. Furthermore, arteriography determines the exact patency of the main vessel at a higher level than we would anticipate by any other tests. In other words, arteriography eliminates any element of doubt as to the site of amputation. We hope, in a subsequent report on amputations with refrigeration, to submit a detailed account of the value and technic of arteriography.

CONCLUSIONS

We have given our experiences in the use of refrigeration for amputation of limbs and also detailed the technic which we generally use. We have enumerated and discussed the fatalities. The mortality rate was higher than in most series of amputations, but the explanation is clear when one considers the cases offered for this method. The incidence of shock was absent in every case. The percentage of gas bacillus infections has been dealt with and is undergoing further study. The general feeling is that the organism lies dormant in the devitalized tissues. The tourniquet has been largely dispensed with in this series. A preliminary discussion on arteriography was included.

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THE BIOPSY AS AN ACCURATE GUIDE TO THE DECISION OF EARLY SKIN GRAFTING

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WHEN A BURN WOUND requires skin grafting, it is desirable that it be done as early as possible.

The reasons for early skin grafting are:

1. To obtain skin coverage as soon as possible in order to prevent disability or loss of life from infection or wasting.
2. To restore the skin surface to a good functional condition.
3. To allow for earliest movement of joints, tendons and muscles.
4. To prevent deformities.
5. For practical economy.

It is important then to have some means of determining whether the wound can be expected to heal spontaneously and satisfactorily, or whether it cannot be expected to heal spontaneously and satisfactorily, and should be skin grafted.

Immediately after the accident, when the patient first comes under observation, it is impossible to be certain to what depth the damage has extended. Even by biopsy, at this stage, the depth of destruction cannot be accurately determined, because heat of an intensity insufficient to cause charring may coagulate and fix the tissue well enough to make it impossible to distinguish between viable and nonviable tissue. Anyway, the assessment of the depth of a burn just after the accident is not important, as primary skin grafting is not practicable except when the burned area is very small. Besides, the condition of the patient usually precludes any surgical procedures of any magnitude other than proper dressings.

Time will reveal, by the reaction of the wound, the true depth of the burn, provided infection is controlled. It will either show sufficiently advanced re-epidermization in the third week, or granulation tissue will appear with no or inadequate epithelization.

This latter state of affairs we believe should not be allowed to go on, because granulation tissue organizes into fibrous tissue, and the longer it grows the more fibrous tissue will be laid down. Even if reepidermization should occur later, the newly formed epidermis will have an underlay of fibrous tissue instead of fibro-elastic corium, *i.e.*, scar skin will form and may prove very unsatisfactory. Indeed, it later may have to be removed and replaced by a skin graft.

At The Montreal General Hospital, the method of treatment used by the burn team,¹ on the Surgical Service of Dr. Fraser B. Gurd, includes the infrequent occlusive compression dressing with an emulsion of sulfathiazol in

an oil-in-water base. This dressing, except in obviously very superficial burns which require no grafting, and heal within one week, is sometimes removed as early as the ninth day. More commonly, however, it is removed about the thirteenth or fourteenth day, with the intention of grafting if necessary, because it is considered that this is the most desirable time to graft, if at all possible. Wound excision may be required. This includes the removal of slough and granulation tissue, if any be present, and even scattered islands of epidermis. But it is by no means easy, even at this stage, to be certain from the gross appearance of the wound, whether it is healing satisfactorily or whether it cannot heal satisfactorily, and will require grafting. Even the most experienced surgeon is prone to err in this matter. The presence on the surface of the wound, of a thin coagulum of exudate masks the true nature of the wound surface.

The study, in the Department of Pathology, over a period of four years, of numerous blocks of tissue, submitted by the burn team from burns in various stages has taught us much about the pathology of burned skin, how it heals and how it may be expected to heal. A direct outcome of this study was the decision, about a year ago, to submit at the time of removal of the first dressing, all questionable cases to biopsy, in order to determine the expectancy of the healing of the wound. It soon became the practice to prepare rapid frozen sections of this tissue at the operating room, and upon the report of the pathologist, the decision to graft or not to graft is made at once. These specimens should be at least 5 Mm. wide to allow for proper handling.

As was pointed out in a previous report,² the healing of a burn depends upon the viable epithelium, in the burned area, available as sources of reepidermization. These sources are the epidermis at the margins of the wound, surface epithelium that has escaped destruction, hair follicles, sebaceous glands and sweat glands.

It was further pointed out that for satisfactory spontaneous healing, there is required at least a sufficient number of hair follicles and sweat glands so that hair follicles, which lie, except in hairy parts, at a higher level than sweat glands, must be spared in sufficient numbers, if spontaneous satisfactory healing is to be obtained. This applies to the donor site as well as to the burn wound.

If destruction should involve most or all of the hair follicles, but spare the sweat glands which lie at a deeper level, spontaneous reepidermization may still be expected, but the process will be slow and it will be attended by the formation of granulation tissue which organizes into fibrous tissue, so that the remains of the viable deep layer of the fibro-elastic corium becomes overlaid by a thick layer of scar tissue covered by hyperkeratotic epidermis—an unsatisfactory result.

If the destruction extends deep enough to involve the sweat glands, there will be no sources of reepidermization other than that at the margins of the wound, and this, in all but very small burned areas, is inadequate.

In doing the biopsies, the finding of destruction of the skin to a level below the hair follicles indicates that satisfactory spontaneous healing cannot be expected, and that skin grafting is required.

On the other hand, if there are viable hair follicles present, spontaneous satisfactory healing can be expected. Usually, at this stage, if viable follicles are present, reepidermization from them and from sweat gland ducts will have already become established if not completed.

The reader may here be reminded that, since the superficial sources of epidermal regeneration either in a burn or donor site, are of the utmost importance, they must be spared and not further damaged by too vigorous handling, by the application of escharotics, by infection, by improper dressings, or by the too early and too frequent changing of dressings.

The method^{1, 2} used by the burn team in this hospital of dressing these wounds has successfully provided for all these requirements. Besides the bacteriostatic sulfathiazol emulsion, the wide-meshed gauze and the infrequently changed compression dressing immobilizes the dressing on the wound surface and thereby prevents slipping of the dressing, and rubbing off of the delicate regenerating epidermis, and it excludes contamination by pathogenic organisms.

The following selected case reports will illustrate the usefulness of the biopsy for guiding the surgeon in the procedure of early skin grafting.

SELECTED CASE REPORTS

Case 1.—A male, age 20, suffered a flame burn on the medial posterior aspect of the right thigh, on April 3, 1944. He was admitted to The Montreal General Hospital about one hour later. A compression dressing with sulfathiazol emulsion was applied.

The dressing was removed on the twelfth day, and as there was some doubt as to the status of the wound, a biopsy was done and the wound was redressed. Paraffin sections (Fig. 1), showed well advanced reepidermization. Hair follicles, sebaceous glands and sweat glands were intact. There was some edema and cellular infiltration just beneath the epidermis, and about the hair follicles. Elastic tissue stains showed elastica right up to the epidermis.

Interpretation: Well advanced, satisfactory spontaneous healing of a superficial burn.

Four days later, on the nineteenth day, the second dressing was removed. Complete reepidermization was then obvious. No further dressing was needed, and the patient was discharged from hospital on the nineteenth day.

Case 2.—A male, age 49, sustained a burn of the face and right forearm by burning fat, on December 22, 1943. He was admitted to hospital six hours later. A compression dressing with sulfathiazol emulsion was applied.

The dressing was removed on the thirteenth day. The opinion of the majority of the surgeons present was that grafting was obligatory. A biopsy was done and a graft was then applied.

A few days later, a paraffin section (Fig. 2) of the biopsy showed quite well advanced reepidermization, but still patchy with unhealed areas. The interpretation was that spontaneous satisfactory healing could be expected. The result was that when the second dressing was removed, fourteen days later, the graft was found to have taken on the small nonhealed areas, but had been lifted up by spontaneous re-

epidermization in the areas of lesser burn depth. A biopsy at this time (Fig. 3) shows the graft separated from the reepidermized wound by a layer of epidermis and desquamated keratin. Wound excision with removal of the graft and healing wound surface was followed by the application of another graft, which took well.

COMMENT.—It is felt that this wound would have healed well spontaneously and without grafting at all.

This patient was in hospital for a total of 44 days, but might have been discharged much earlier had the wound been allowed to heal spontaneously.

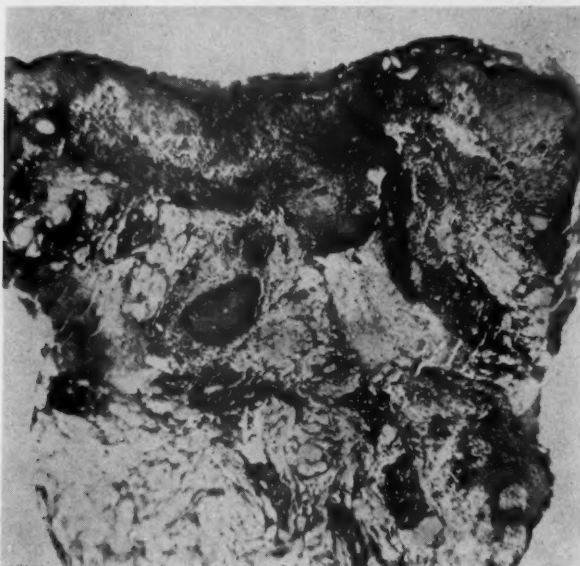


FIG. 1.—Case 1: Biopsy, 12th day. Reepidermization is complete. There is a viable hair follicle in the centre of the field and part of one at the lower right margin.

There is moderate inflammatory cell infiltration and edema still present in the corium. On the surface there is a thin layer of coagulated exudate.

The experience with these two cases led to the practice of not proceeding with the graft at this early stage without confirmatory histologic evidence of the status of the wound, which can be obtained by biopsies, and at once by quick frozen sections.

Case 3.—A male child, three years old, sustained a 30 to 35 per cent hot water burn involving the right side of the trunk, right arm, right leg and part of the left leg and the right hand. The wound was dressed as usual.

On removal of the first dressing on the fourteenth day, there was complete healing of all parts, except for a 5- x 3.5-inch area in the midpart of the right side of the chest. Several experienced surgeons, including visitors, said that grafting was not necessary. A biopsy was done and the area was redressed.

Paraffin sections (Fig. 4) revealed a deep burn in which there were no recognizable follicles or sweat glands, and no evidence of reepidermization. There was intense inflammatory cell infiltration throughout the corium and in the subjacent fat.

The interpretation was "deep burn" with no possible sources of reepidermization.

FIG. 2

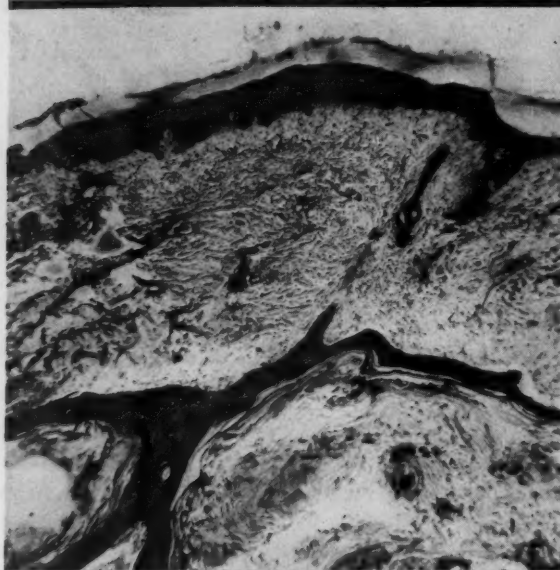
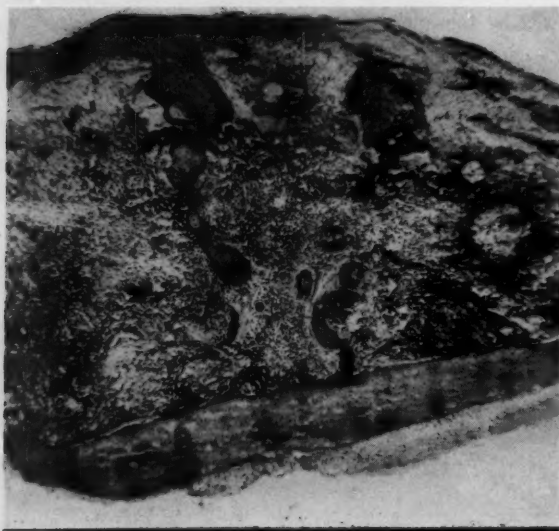


FIG. 3

FIG. 2.—Case 2: Biopsy, 13th day. There are viable hair follicles and sweat gland ducts from which reepidermization had spread over most of the surface.

There is also marked inflammatory cell infiltration and slight edema of the corium.

The bar along the lower margin of the section is fresh blood clot.

FIG. 3.—Case 2: Biopsy, 27th day, 14 days after grafting. Note the spontaneously regenerated epidermis under the graft separating it from the healing wound.

Removal of the dressing was unnecessarily delayed until the twenty-fifth day, and a graft was applied. The patient was ready to be sent home on the thirty-seventh day, but was retained in hospital until the forty-fifth day for other reasons.

FIG. 4

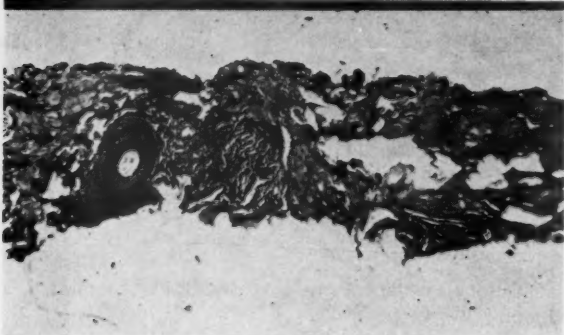
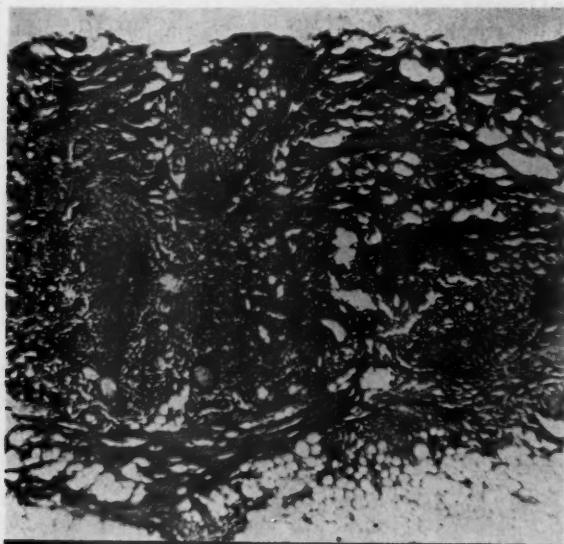


FIG. 5

FIG. 4.—Case 3: Biopsy, 14th day. There are no surface epithelium, hair follicles, or sweat glands recognizable. There is intense inflammatory cell infiltration which extends into the subcutaneous fat. Destruction has extended to practically the full depth of the skin. Spontaneous healing could not be expected.

FIG. 5.—Case 4: Biopsy, 9th day, paraffin section. To the left is a viable hair follicle, but to the right there are no follicles or sweat glands. In the rapid frozen sections there was regenerated surface epithelium only over the end containing hair follicles. This was lost in the handling of the biopsy in the preparation of the frozen sections.

Case 4.—A male, age 38, received a flash burn of the face and upper extremities on the day of admission, June 19, 1944. The wound was covered by a compression sulfathiazol dressing. On the ninth day healing was found complete, except for an area of 3 x 4 inches just above the elbow on the extensor surface.

A biopsy was done in a radial axis at the periphery of the wound. The frozen section showed hair follicles and reepidermization at the outer end, but in the remainder of the section, destruction had extended down to the sweat glands.

A graft was then applied over the whole area, with a good take, except at the periphery where spontaneous healing occurred. The patient was discharged on the twenty-ninth day.

Later paraffin sections (Fig. 5), show the deep destruction at one end and a viable hair follicle at the other. The surface epithelium seen here in the frozen sections, is not present in the paraffin sections. In the deeply destroyed area, there is inflammatory cell infiltration in the remains of the corium, and along the subjacent margin of the subcutaneous fat.

The interpretation of this biopsy is that marginal healing was in progress

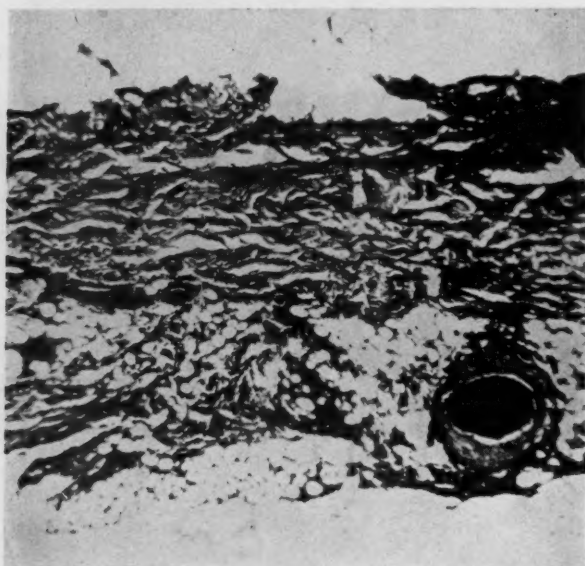


FIG. 6.—Case 6: Biopsy, 13th day. Only a strip of the base of the corium remains and there are no follicles or sweat glands. There is moderate inflammatory cell infiltration in the subcutaneous fat.

Note the artery plugged with coagulated blood.

but beyond this satisfactory spontaneous healing could not be expected, and that grafting should be carried out.

Case 5.—An adult male, age 44. On admission there was a seven-day-old 4- x 5-inch steam-jet, infected burn over the right deltoid region. A compression sulfathiazol dressing was applied, and four days later (eleventh day), it was taken down.

A biopsy by frozen sections revealed a deep burn with no sources of reepidermization. A graft was applied. The patient was discharged on the seventeenth day.

Case 6.—A male, age 47, sustained a burn by molten steel on the face, left wrist and right foot, which was treated by compression dressing and sulfathiazol emulsion. On the thirteenth day the dressings were removed, and healing was found complete except for a 3- x 4-inch area on the dorsilateral aspect of the right foot. The status of this wound was doubtful.

Biopsies by frozen sections (later confirmed by paraffin sections [Fig. 6]), revealed a deep burn with no sources of epithelium available for reepidermization.

The wound was excised down to a satisfactory level, and a graft was applied. The dressing was removed on the twenty-sixth day when there was a 100 per cent take of the graft. The patient could have been discharged on the twenty-eighth day, but was held until the thirty-eighth day for investigation of neurosyphilis.

BIOPSY AS GUIDE FOR SKIN GRAFTING

SUMMARY

The desirability of the use of biopsies in the management of early skin grafting of burns is discussed and six selected cases are cited as illustrations. All these wounds were undressed between the ninth and fourteenth day with the intention of grafting if necessary. Biopsies were done on all six cases because of doubt as to the status of the wounds. In the first three cases delayed paraffin sections were used, and in the last three, rapid frozen sections and delayed paraffin sections were employed. In Case 1, the biopsy showed well-advanced healing and no grafting was needed. In Case 2, the biopsy and grafting were done at the same time. Later, the examination of the biopsy indicated that grafting was not needed and this was borne out by the subsequent behavior of the graft. In Case 3, after biopsy on the fourteenth day, the wound was redressed to await the report on the paraffin sections. This indicated the necessity of grafting, which was not done until the twenty-fifth day—an unnecessary delay. Had a frozen section been made, grafting might have been done on the fourteenth day. In Cases 4, 5 and 6, rapid frozen section biopsies at the time of removing the first dressing on the eighth, eleventh and thirteenth day, respectively, all indicated the necessity of grafting, which was carried out without further delay, and with entirely satisfactory results.

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SKIN GRAFT OF DORSUM OF HAND

USE OF LARGE SIZE DERMATOME* TO OBTAIN ONE-PIECE PATTERN

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EXTENSIVE WAR BURNS of the hand involving the deeper layers of the dermis and the full-thickness of the skin have required total replacement of the skin of the dorsum by skin grafts of intermediate thickness. In such cases, a considerable area of skin graft is required to restore normal flexion and function of the hand and fingers. At least two pieces of skin graft usually are needed when the graft is cut free-hand and often when it is cut with Padgett's dermatome. It is not infrequent to see the junction scar-line between the graft become hypertrophic or even cheloidal; such scars not only are unaesthetic but also may impair the function of the hand. It became apparent, therefore, that the use of a large one-piece skin graft accurately cut and fitted according to a pattern was desirable. A large drum (Fig. 1) which could be fitted over the ordinary Padgett dermatome was constructed. With this drum a piece of skin graft covering the area of the drum (8 x 6 inches) may be removed when cut transversely across the thigh. After the dorsal scar of the hand and fingers has been completely excised, a pattern of the resulting defect is made, the hand being maintained by a splint in a position which is close to the position of function, but which permits the application of the largest piece of skin graft with the fingers and wrist in semiflexion (Fig. 2). This pattern is then reversed and applied to the raw surface of the skin graft on the drum (Fig. 3). A pattern graft is cut by incising the skin graft on the drum with a scalpel, following the contour of the pattern. The skin graft is removed from the drum; while this procedure is being done, fine sulfanilamide powder is rubbed over its cemented surface to neutralize the cement, and prevent the adhesion of the graft to itself. The skin graft is applied to the raw area, fixed by a few interrupted sutures and its edges are sutured to the edges of the defect by a continuous running suture of fine silk. A pressure dressing is then applied over the skin graft in the usual manner with cotton or mechanics waste.

* The large drum shown in Figure 1 was made two years ago for the author by Thackeray & Sons, London, England.

† At present Captain, Medical Corps, U. S. Army.

FIG. 1A

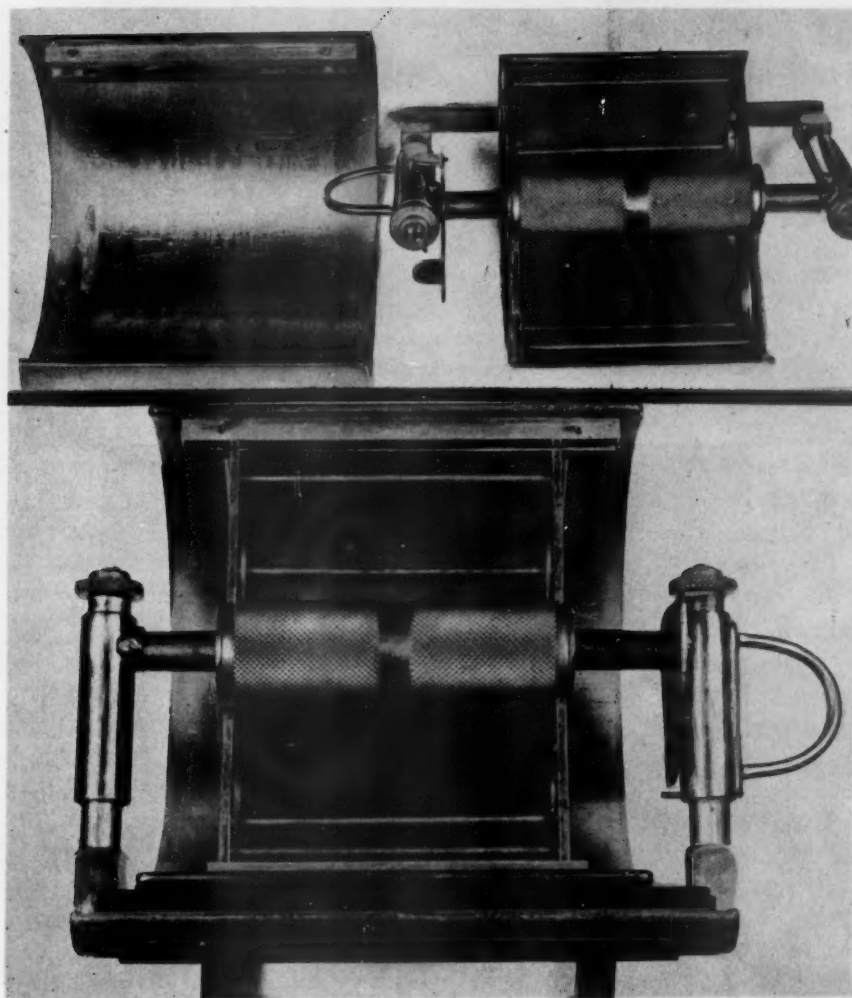


FIG. 1B

FIG. 1A.—On the left is shown the large drum (8 × 6 inches) which is made to fit accurately over the drum of Padgett's dermatome (on the right).

FIG. 1B.—The large drum has been fitted over the drum of Padgett's dermatome to which it is held by a spring clamp. (Note: Small dots on photograph indicate this spring clamp.)

FIG. 2



FIG. 3

FIG. 2.—Dorsum of the hand after the excision of all of the cutaneous and subcutaneous scar. The hand is immobilized in this position by a splint. A pattern is made of the defect which extends around the radial aspect of the thumb and around the ulnar border of the hand.

FIG. 3.—The pattern of the defect is reversed and applied to the raw surface of the skin graft on the drum. A one-piece pattern skin graft may now be cut by incising the graft around the pattern. The excised scar is shown below the drum. (Note: This is the scar tissue excised from the hand—not the graft.)

PROXIMAL LIGATION AND THROMBECTOMY FOR PHLEBOTHROMBOSIS OF THE FEMORAL AND ILIAC VEINS*

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THE TREATMENT OF PHLEBOTHROMBOSIS by thrombectomy is not an unchallenged procedure. There are many who feel that if the patient is properly treated with anticoagulants operation is unnecessary. By thrombectomy I mean the removal of the clot from the iliac vein as it extends above the inguinal ligament. Even among surgeons there is a more radical group who believe in proximal ligation even if the vena cava itself has to be ligated. All methods of therapy are directed toward eliminating pulmonary embolism.

May I state that I believe more lives will be saved by thrombectomy than by the use of anticoagulants alone. The literature in recent years has brought forward advocates of the thrombectomy treatment. Fine, Homans, Arthur Allen, and his group, are all advocates of this procedure. While I have had only a limited experience, nevertheless, I believe a careful analysis of this small series may prove of value. In presenting this subject I wish to discuss briefly the pathology, in order that we understand the limitations of this discussion.

In the long veins of the extremities there are two processes that occur largely postoperative. These two processes are usually clear-cut; but they sometimes merge one into the other. These processes are thrombophlebitis and phlebothrombosis.

Thrombophlebitis, as the name indicates, is a phlebitis and periphlebitis associated by sometimes an absence of a clot in the lumen. It is usually initiated with a chill, high temperature, swelling of the leg, marked tenderness, and often redness over the course of the involved vein. It is characterized very largely by perilymphatic involvement, as well as involvement of the walls of the vein. Embolism following thrombophlebitis is relatively rare. It occurred in 10 per cent of the Toronto series and about 12 per cent of the series analyzed by the Mayo Clinic.

Phlebothrombosis is characterized by a blood clot which fills the lumen of the vessel. The onset may be sudden. It is not accompanied, as a rule, with as high elevation of temperature or with as great swelling of the leg as in thrombophlebitis. Homans has shown experimentally that if one wishes to create a so-called *alba dolens* in experimental animals it is necessary to destroy the lymphatics. Mere ligation of the vein will not, as a rule, create swelling.

In this presentation I wish to discuss the latter of the above two subjects and discuss it largely as a means of preventing the formation of pulmonary

* Read before the Philadelphia Academy of Surgery, November 6, 1944.

embolism, for it is in this type that emboli are more frequent. Symptoms may be silent and not recognized until after the embolus has separated. I wish also to discuss the two methods of operative procedures, *vis*: Proximal ligation; and (2) thrombectomy.

Proximal Ligation.—This is performed when the clot in the vein has not extended upward as far as the inguinal ligament. This is of course a safe procedure and one which, in my opinion, should be undertaken much more often than it is. The patient can then be immediately mobilized without fear.

Thrombectomy.—When the thrombus has extended beyond the iliac ligament, thrombectomy may be performed by mechanical removal, such as using thin, narrow forceps for extraction, or by suction. I wish to concentrate on the latter procedure, and to analyze a series of cases I personally have had, and give you my reactions and results. The purpose of this operation is to avoid pulmonary embolism. Obviously, thrombosis, if there were no complications by embolism, would not be a very serious condition. It would cause swelling of the leg and some disability for a period of time. We all have seen many cases that have not had proximal ligation that have gone on to recanalization and complete recovery of the patient.

In my own series of 12 cases of thrombectomy from the iliac veins, eight have suffered from pulmonary emboli, and four have no outward evidence of embolism. Where thrombectomy has been performed, the use of an anticoagulant postoperative seems necessary. With proximal ligation, where one is above the clot, one does not fear particularly the recurrence of the disease except in patients who suffer from the migratory type of phlebotrombosis. I have had a much larger series where this procedure has been carried out without mortality, but am not reporting on them at this time. Where a thrombus has been removed above Poupart's ligament by suction or traction from below, it is obvious that a ligature is not applied proximal to the site where the clot was located. Therefore, it is advisable to use anticoagulants to prevent further thrombosis.

DIAGNOSIS

When a patient postoperatively is running a slightly irregular temperature, it is wise to pay attention to the foot, calf, and thigh. Homans has described the sign, which is now given his name; if the foot is flexed dorsally it compresses the gastrocnemius muscle, and pain is experienced in the calf. I have also found that if one semiflexes both knees, with the feet resting on the bed, the calf of the affected side gives one the feeling of a deep edema, and, as the gastrocnemius muscle is compressed against the posterior surface of the tibia, pain is elicited. Compression of the popliteal space may also present a tender area; or, if one passes the index finger horizontally across the thigh, pain is elicited over the course of either the long saphenous or Hunter's canal. On coming to Poupart's ligament the femoral artery does not give as clear a pulsation as on the noninvolved side, and beneath the artery may be felt a lead pencil-like cord, which is the thrombus in the femoral vein.

While venography has been advocated by Fine, and others, it is frequently difficult to determine whether the defect noted on the roentgenogram is due to venospasm or occlusion of the vein. Almost always, one can tell by physical examination, in the acute emergencies, more than one can tell from venography.

INDICATIONS FOR OPERATION

1. *Pulmonary Embolus with Evidence of Phlebothrombosis of the Veins of the Leg:* If proximal ligation is possible there is no question but that this is the operation of choice and the treatment of choice, because it allows immediate mobilization of the patient without fear of the extension of the disease. If the thrombus extends above the iliac ligament, I believe that extraction of the clot, either by manual extraction or suction, followed by bisection and removal of a section of the femoral vein is the procedure of choice.

2. *Phlebothrombosis without any Evidence of Embolism:* There are three methods of therapy that may be carried out when the diagnosis of phlebothrombosis of the deep femoral vein which extends upward into the iliac vein has been made. They are: First, incision of the vein and removal of the clot—phlebectomy. Second, the use of anticoagulants without surgical procedure. Murray, in Gallie's clinic in Toronto, has listed 18 successful cases of pulmonary embolism that have been treated by heparin without further evidence of pulmonary embolism. Others have not had as successful an experience. There have been a number of cases reported where death from embolism has occurred after heparinization has been discontinued. I had a case of my own that died from pulmonary embolism two days after heparin was discontinued. Third, novocaine block of the first to fourth lumbar ganglia. Leriche advocated this procedure primarily, and in this country it has been strongly advocated by Alton Ochsner. I quote from Ochsner's article to give you, better than I could brief it, the mechanism of this procedure:

"In previous publications we have discussed in detail the mechanism by which venospasm and thrombophlebitis can produce clinical manifestations. Edema may be due to factors that result from venospasm and increase the amount of perivascular fluid; increased filtration pressure; anoxia of the capillary endothelium; and diminution in the flow of lymph. The increase in venous pressure in thrombophlebitis has been repeatedly demonstrated. This obviously increases the filtration pressure, which favors transudation of fluid from the vascular into the perivascular spaces. Because of the associated arteriolar spasm and evidence of diminished vascularity, there probably occurs an anoxia of the capillary endothelium that increases its permeability, permitting an excessive exudation of fluid into the perivascular spaces and thus resulting in the production of edema. Once the fluid gets out of the vascular channels in such a case it has difficulty in getting back because of the increase in the pressure on the venous side. Probably of greater significance in this condition is the fact that the pump, which is responsible for the movement of the lymph, is lost. Several investigators have demonstrated that the movement of lymph is dependent on arteriolar pulsations. In the presence of marked venospasm and increased venous pressure, arteriolar pulsations are reduced to a minimum, and the lymphatic pump is thereby lost.

"This decrease in lymph flow results in the stagnation of the lymph fluid and the

accumulation of proteins in the perivascular fields, thus setting up a vicious circle, in that the pressure of the perivascular fluid approaches that of the intravascular field, tending to prevent absorption of fluid from the perivascular spaces into vascular channels. Such a vicious circle is broken by novocaine block of the sympathetic ganglia, which causes an interruption of the vasoconstricting impulses and thus produces a reestablishment of the normal exchange of the intravascular and perivascular fluids. It has been demonstrated that blocking of the sympathetic nerves increases the flow of lymph. As a result of vasodilatation, the blood supply to the capillaries is increased, anoxia of the capillary endothelium is relieved, and excessive exudation of the vascular fluid into the perivascular spaces is prevented. By the return of the normal arteriolar pulsations, the pump, which is responsible for the movement of lymph, is reestablished, and the perivascular fluid is rapidly carried away. Because of this, the edema of the extremity in a patient with phlegmasia alba dolens disappears within a relatively short time after the production of sympathetic ganglion block.

"Similarly, the other manifestations associated with thrombophlebitis are relieved, probably by the increased vascularity. Pain, which is one of the most prominent manifestations of thrombophlebitis, is relieved dramatically. Prompt subsidence of fever may also be explained on the basis of a more rapid resolution of the inflammatory process by the increase of vascularity to the involved venous segment."

Of these three methods I prefer thrombectomy, although I am free to admit that a certain number of unnecessary operations will be performed. If the patient is seen early after the initiation of the disease, thrombectomy is a relatively safe procedure, and is apt to eliminate the danger of pulmonary embolism. However, when the patient is first seen eight to ten days after the onset of phlebothrombosis, and where no evidence of pulmonary embolus has been present, I believe that we are safe in following a conservative course. It has been my experience that embolism usually occurs early in the course of thrombosis—occasionally even before its presence may have been diagnosed—in the thigh or leg, and that it is not as apt to occur after the clot has been formally organized. In the small series of eight cases that I have seen of this type no pulmonary embolus has developed.

OPERATIVE TECHNIC

Anesthesia.—In many cases there has been pulmonary embolism of sufficient severity to contraindicate against general anesthesia. In such cases local anesthesia seems to be the one of choice. There is danger, as is shown in Case 12 of this series, that the position necessary for spinal anesthesia, with flexion of the thigh on the abdomen, might cause dissociation of a thrombus. Cyclopropane, where the case is early and without embolism, or with only slight evidence of pulmonary involvement, is also easier on the operator and the patient. *Local Anesthesia:* No matter how carefully one blocks the field with novocaine there is a time when the vein is being separated from the artery that pain is present and cannot well be eliminated. Lumbar block might help at this time. When one opens the femoral sheath below Poupart's, in the cases I have operated upon there is a sticky, gelatinous adhesion of the artery and vein, and it is with considerable difficulty that the vein is sufficiently separated from the artery to allow an aneurysm needle to be placed about it and a traction ligature applied.

It has been my habit to expose the vein about an inch below Poupart's so as not to ligate below the profunda branch of the vein. After a traction ligature above and below has been placed, a longitudinal incision is made into the vein. The nearby blood clot is removed by forceps. Then a glass tube attached to a suction machine is inserted into the vein and passed upwards beneath Poupart's ligament until the thrombus has been removed and free bleeding occurs. If the tube is not long enough to permit free bleeding, a rubber catheter is attached and this is passed upward until one is certain that it has gone beyond the bifurcation of the vena cava. It is difficult, in the lower portion, to get enough suction to excise the clot through the smaller lumen of a catheter. A glass tube in this lower portion is much more efficient. I am convinced that the suction must be applied until free bleeding occurs. After the clot has been removed, the vein is doubly ligated on each end of the incision. The intermediary portion is removed. It is advisable at this time to look for the long saphenous, as it may also contain a clot, and, if so, it should be tied at its junction with the femoral vein. Usually I have ligated and cut both the long saphenous and femoral veins. If the femoral vein at the initial exposure is found in spasm, with only a small clot in its lumen, the long saphenous should be looked for. In two of my patients the clot extended up the long saphenous and thence into the femoral vein and upward into the iliac. The femoral vein itself was in spasm, with only a small clot within its lumen.

The use of anticoagulants is necessary in order to prevent the reformation of a thrombus above the ligated vein.

In this series of 12 cases, continuous intravenous heparin has been used in 5, dicoumarol in 2, and subcutaneous heparin, as described by Loewe, in 5.

In reviewing the following cases I have mentioned only those in whom thrombectomy of the iliac vein has been performed. Of the 12 cases, eight have had antecedent emboli, and four had no evidence of embolism. In this series, three had simultaneous thrombectomy and ligation of both femoral veins. One patient had a thrombectomy immediately preceding operation, and another case a thrombectomy two weeks previous to a supracervical hysterectomy.

CASE REPORTS

Case 1.—A musician, a woman of about 50, had received a bumper fracture of the tibia. She had been treated by another surgeon. After her return home she had 12 pulmonary emboli—two nearly fatal ones. She had been treated by heparin intravenously for one week before I saw her but had shot one small embolus during this time. Her left leg and thigh were markedly swollen. There was only moderate elevation of temperature. In bed at home, under light gas anesthesia, the femoral vein was first exposed. It was in spasm and contained only a very small clot. It was doubly ligated and cut below the entrance of the profunda branch. The long saphenous was then exposed. It contained a large thrombus, which on exposure was found to extend into the iliac vein. The saphenous vein was opened, as much of the clot extracted as could be done with forceps, then a glass suction tube was passed upward into the femoral vein. Clots were extracted until the tube was passed upward about six inches,

when free bleeding occurred. The vein was doubly ligated and cut. Heparin was continued for three days. Her temperature rapidly subsided. In five days her left thigh and calf were the same size as the normal leg. Her convalescence was uneventful, and she had no more emboli, nor has she any residual swelling of the leg.

Case 2.—A woman of 45, who had been ill at home with acute cholecystitis ten days before I saw her. At operation, I found a gangrenous gallbladder, with a perforated abscess in the liver. Cholecystectomy, with drainage, was performed. On the third postoperative day it was noted she had a swollen left leg and thigh. The long saphenous was palpable as a tender cord about the size of a lead pencil. On the fourth postoperative day she was operated upon and, under cyclopropape anesthesia, the femoral and long saphenous veins were exposed. Both contained large thrombi. By suction, a propagating thrombus about five inches long was removed from the iliac vein above Poupart's ligament. Both veins were doubly ligated and cut. She was treated with dicoumarin until her prothrombin index was one-third of normal, when it was discontinued. Her convalescence was uneventful until ten days later when she developed an acute phlebitis in the calf of the leg operated upon, associated with a chill, elevation of temperature, leukocytosis, and swelling and tenderness of the calf. The attack subsided under elevation and sulfa therapy. She had a residual swelling in the calf upon leaving the hospital. At present there is still some swelling of the calf.

Case 3.—A young woman who had had an amputation of her left thigh at Memorial Hospital, for sarcoma. I saw her with Dr. Stanley-Brown. She developed swelling of both thighs and shot two pulmonary emboli—left, then right. Both femoral veins were exposed simultaneously, under local anesthesia. On my side (the amputated one) no clot was encountered, but there was evidence of phlebitis. On Dr. Stanley-Brown's side a clot was encountered extending well up into the iliac vein. A similar procedure was carried out as in the other cases. Heparin was administered five days postoperatively. Her convalescence was uneventful, and the swelling rapidly subsided in both sides.

Case 4.—A woman of 53, upon whom a supravaginal hysterectomy had been performed by another surgeon four weeks previously. For the previous two weeks before I saw her she had had pulmonary embolic seizures, confirmed roentgenologically, and by Dr. James Miller and Dr. Harold Hyman. There was fluid at the right base. The left calf and thigh were moderately swollen. She was operated upon. Under local anesthesia, the femoral vein was exposed. It was occluded with clot, but the long saphenous vein was not involved. The clot extended upward about seven inches in the iliac vein. The same operative procedure was carried out, but, in addition, she had a lumbar ganglion block with novocaine. She had a moderate infection of the fat at the operative site in the thigh. She was given heparin subcutaneously by Loewe's method. Her convalescence was uneventful, and she had no residual swelling.

Case 5.—A 68-year-old female, with a large ovarian carcinoma, had evidence of a thrombus in her right femoral and saphenous veins. At the time of operation a thrombus was removed from her right iliac vein and then a bilateral oophorectomy for tumors the size of a football was performed. She died on her 15th postoperative day from renal failure. There was no residual swelling of the leg or signs of pulmonary condition. No autopsy was obtained.

Case 6.—A suprapubic prostatectomy was performed upon a 60-year-old man at Beth David Hospital. Postoperatively, while in the hospital, he shot several pulmonary emboli, and swelling of the left thigh and calf was noted. Despite this fact he was allowed to go home. After his return home he had several other episodes of pulmonary emboli. He was seen at home by Dr. Solomon, who recommended his return to the hospital for thrombectomy. I saw him later at home and made the same recommendation. He was readmitted to the hospital. He was cyanotic, dyspneic, and had fluid at the right base. A similar operative procedure was carried out. He was treated first with

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heparin and later, at Doctor Solomon's suggestion, with dicoumarol. His convalescence was remarkably uneventful after his dyspnea subsided, about four days postoperative.

Case 7.—This patient had a supracervical hysterectomy three weeks previously. During the past week she had had three definite small pulmonary emboli. The left femoral vein contained a thrombus extending well above the inguinal ligament. A long thrombus above Poupart's was removed by suction. She was treated by subcutaneous heparin. She had some residual pain in the leg, but no swelling, for six weeks postoperative.

Case 8.—A woman seen with Doctor Stanley-Brown at the New York Hospital. The patient was 62 years of age. She had had a coronary embolism in 1939. In February of 1943 she had a second coronary attack with three pulmonary infarctions. On April 14, 1943, she complained of pain in the right popliteal vein. On the 16th of April, heparin was started. On the 19th, I was called to see her by Doctor Stanley-Brown, and we found there was evidence of phlebothrombosis in both femoral veins. The femoral veins were exposed under local anesthesia. On the left side the vein was in spasm, and contained only a string-like clot. It was opened and a small clot sucked out of the lumen, and the vein then ligated. On the right side a long clot, extending well up toward the bifurcation of the vena cava, was removed. Both veins were doubly ligated and cut. Heparin was administered two days postoperatively, and the patient had an uneventful recovery. She was seen a year and a half afterward, at which time no swelling was noted in either thigh or leg.

Case 9.—This patient had a normal delivery of a child on April 19, 1944. On April 25th swelling was noted in the left leg and thigh, and she had an attack of pain in the chest on May 9th. The patient was kept in bed and treated with rest. On May 15th, pain and swelling appeared in the right leg and the patient had another attack of pain in the chest. Under local anesthesia, both veins were exposed, and a clot was sucked out of each long saphenous and each femoral vein. Heparinization was administered for five days postoperative. Convalescence after this was uneventful, save that she had considerable swelling of both thighs, which persisted for six weeks. In a late follow-up I have learned that she is playing tennis, and, therefore, it is obvious that the swelling must have become greatly reduced.

Case 10.—A woman of 46 had been seen by a gynecologist, who recommended hysterectomy for an extremely tender uterine fibroma which was fixed in the lower portion of the pelvis. The uterus extended midway to the umbilicus. Ten days later, while awaiting operation, acute phlebothrombosis occurred in the left femoral vein. I was called to see the patient at this time. There was no evidence then of pulmonary embolism. It was felt, however, that this patient would need hysterectomy in the near future because of a degenerating fibroid, and that it would be advisable to be sure that the clot was removed from the iliac vein. The clot was sucked out from the left iliac vein, and she was treated postoperatively by subcutaneous injections of heparin. Two weeks later, while still under heparinization, a supracervical hysterectomy was performed. The iliac vein was palpated and there was no evidence of any clot in its lumen. There were, however, some old thrombi in the veins of the broad ligament. This patient's convalescence was uneventful. She left the hospital two weeks after the hysterectomy.

COMMENT: This patient was one of the few cases I have known where inspection occurred within two weeks of a thrombectomy. No evidence could be seen by the operating surgeon of occlusion of the vein.

Case 11.—This patient had a cesarian section performed for a premature separation of the placenta in a seven-month pregnancy. A live baby resulted, and the postoperative convalescence of the mother was unusually smooth. There was no postoperative elevation of temperature; there was no complaint of abdominal or thigh pain.

The patient left the hospital on the 12th postoperative day. Three days later she complained of an acute attack of pain in the chest. She was readmitted to the hospital. Her temperature rose to 103° F. Three days after admission roentgenograms of the left chest showed irregular consolidation. Her physician had carefully gone over both legs and thighs; there was no difference in their circumference. There was no tenderness. Ten days after her admission into the hospital she had a sudden swelling and pain in the left thigh. I was called to see her on the next day. Under local anesthesia, the left femoral vein was exposed. A clot was removed. I did not feel, however, that I had reached the upper end of the clot because free bleeding was not obtained. It was in a strange hospital; there was some difficulty in getting the proper kind of tube, and I did not insert a catheter, as I should have, high up in the iliac vein, and I did not get as free bleeding as I wished. Her postoperative course was improved for about six days. Her temperature receded to almost normal, and she had no pain or swelling in the leg. However, eight days after the thrombectomy she had a sudden attack of pain in the right chest, with elevation of temperature. Roentgenograms showed a cloudy right lung, with not as great consolidation as on the other side. Up to this time there had been a question whether this was a virus pneumonia followed by a phlebothrombosis, or whether the initial infarct antedated the appearance of the phlebothrombosis by ten days. Eight days after the second attack of pain in the chest, phlebothrombosis developed in the right thigh. This time, under spinal anesthesia, a clot was removed from the left femoral vein, followed by free bleeding. The patient, however, went into collapse. She started to go into collapse during the administration of a low spinal, and her collapse continued after the removal of the clot. She was returned to her room in a serious condition. She lived three days thereafter.

Autopsy.—*Lungs:* The right lung is completely collapsed and attached to the chest wall by numerous strands of fibrin and purulent exudate. There are about 500 cc. of a fibropurulent fluid in the right pleural cavity. The right lung weighed 400 Gm. The left lung is adherent at the apex to the chest wall by old fibrous adhesions. About 100 cc. of thick purulent exudate are present in the left pleural cavity. The left lower lobe is completely collapsed. The left upper lobe is well aerated and pink in color. Examination of the branches of the pulmonary artery show a large thrombus in the lumen of the right vessels, with branches running to all of the lobes. This thrombus is yellow in color and adherent to the intimal layer of the vessel. On the left side there is a similar-appearing thrombus in the lumen of the branch of the left pulmonary artery leading to the left lower lobe. There is no thrombus found in the lumen of the main pulmonary artery. No mediastinal node enlargement is found.

Uterus: The uterus is small and anteverted. The operative wound in the anterior wall of the myometrium is well closed by chromic catgut sutures, which are still present. Adherent to the anterior surface of endometrium is some granular pink tissue which grossly resembles placental tissue. The tubes and ovaries are essentially normal. The veins in the broad ligament of the right side are natural. On the left side the vessels at the base of the broad ligament contain distinct well-organized thrombic tissue. The vena cava and both iliac veins are opened. The right vein contains some postmortem clot which is lying free in the lumen of the vessel. On the left side, however, the blood clot in the iliac vein is well organized, yellowish-pink in color and adherent to the vessel wall. The thrombus runs up into the vena cava for a distance of 3 cm. At the upper end of this thrombus the blood clot is distinctly postmortem in nature. The branch of the hypogastric vein leading from the left iliac vessel is also thrombosed as are those of the veins in the pelvis on the left side. In the region of the left femoral vein the thrombus in the lumen of the vessels appears relatively fresh but distinctly postmortem."

COMMENT: My impression of this case is that if I had been successful in removing the clot on the left side there probably would not have been an

extension of the process to the right side nor would there have been the later casting off of emboli. The unusual picture in this case was the time element, the development of the signs of the thigh ten days after the original infarct in each case. This was obviously a case which showered emboli from the pelvic veins, although on examination of the uterus there was no evidence of broad ligament involvement.

Case 12.—A male, age 55, was operated upon for an inguinal hernia six years ago. His convalescence was complicated by a thrombophlebitis of the left thigh and leg. I am unable to determine whether this was a deep or superficial phlebitis. Following his convalescence he was well until six weeks ago, when he had an attack of phlebothrombosis of the superficial veins below the knee. After two weeks rest in bed he was allowed up. After being up and about for a week the process extended to the long saphenous vein. He was put to bed again for three weeks, with elevation and local heat. The phlebothrombosis gradually extended to the saphenous triangle. The day before I saw him he had a sudden severe attack of pain in his right chest, accompanied by shortness of breath but no bloody sputum. He was transferred to a hospital and operated upon. The long saphenous vein contained a clot which extended into the iliac vein. The femoral vein was exposed distally. It did not contain any thrombus. The thrombus was sucked out of the iliac vein and the saphenous was ligated and a portion excised. He was given heparin in Pitkin's solution, intramuscularly. His convalescence was uneventful.

COMMENT: In the early stage it would have been so easy and safe to perform, under local anesthesia, a proximal ligation on this patient. He would have been saved weeks in bed, as he could have been mobilized immediately postoperative.

SUMMARY OF CASES

Twelve cases with 16 thrombectomies, including three simultaneous thrombectomies of both iliac veins, are reviewed. Case II, with first a thrombectomy on the left side, and then, ten days later, a thrombectomy on the right, is reported as two operations because of the intervening time element. Two thrombectomies preceded operation; one immediately preoperative (the case of the carcinoma of the ovary), and the second two weeks before hysterectomy.

There were two deaths in this series; one not due to the disease, the patient dying two weeks postoperative of renal insufficiency. The second death was definitely due to the disease.

Only one patient had a later embolism.

Anticoagulants were used in all of the cases.

I should like to describe the method of using heparin subcutaneously, by injections at 2- to 3-day intervals, as developed by Leo Loewe, in New York. I quote from Loewe as follows:

"To accomplish a slower and more equitable absorption of heparin, the Pitkin menstruum was adopted as a vehicle. This menstruum was developed to regulate the rate of release of water soluble drugs injected intramuscularly or subcutaneously. The ingredients are gelatin, 15 to 30 per cent; dextrose, 5 to 12 per cent; acetic acid, 1 to 1.5 per cent; distilled water, q.s. to 100 per cent. The viscosity of the menstruum, which is predicated on the concentration of the gelatin and dextrose, determines the

rate of liberation of the drug; the greater the viscosity, the slower the liberation. In the preparations containing heparin the optimum percentages of gelatin and dextrose were 18 per cent and 8 per cent, respectively.

"Ampules containing varying proportions of heparin and Pitkin menstruum, with or without vasoconstrictor elements, were prepared. All ingredients apart from heparin were found to be inactive in control tests.

"The contents of the ampules were liquefied at 110° F., drawn up through a 2.5-inch, 19-gauge needle into a previously warmed, sterile 5 cc. or 10 cc. syringe and immediately injected subcutaneously, preferably in the anterior or lateral aspect of the thigh. Intragluteal injections were also done in a limited number of instances. Although this method of administration was abandoned because of too rapid absorption, further experience may eventually prove it to be just as effective as by the subcutaneous route. When two ampules were employed, the contents were thoroughly admixed in the syringe before injecting. The material congealed promptly following inoculation. The injections were administered with a minimal amount of discomfort to the patient. Some patients subsequently complained of pain, tenderness, and swelling at the site of inoculation, particularly when a large amount (3 to 4 cc.) of the menstruum was used. This, however, did not prove to be a deterrent to further treatment, and symptoms promptly subsided upon cessation of therapy."

The results of Loewe's treatment are that it is possible now to heparinize a patient for ten days at a much less expense and with possibly three to four subcutaneous injections during this time.

My observations of Loewe's method show that it does lengthen the bleeding time, and that the patient has no ill effects from the treatment save for the pain in the injection area. This tenderness in the area where the heparin-Pitkin solution is injected becomes quite a problem as the patient may, about the time of the third injection, oppose the injection because of the pain involved. As the process is improved, however, I feel certain that this one difficulty will be remedied. To those who have had to give heparin constantly for from five to ten days, this method is a great improvement. The expense of the old method, and the amount of fluid given during each 24 hours, almost make continuous injection prohibitive in these days of diminished nursing care.

SUMMARY AND CONCLUSIONS

Twelve cases of thrombectomy of the iliac vein have been presented. Three of these thrombectomies were performed as bilateral excision of clot in each iliac vein. In this group there was one mortality due to an embolus. The postmortem examination and case history of this case are presented and discussed. It is the author's opinion that this procedure is safe, that it does not result in marked swelling of the leg, and is a life-saving measure in cases where emboli have already resulted.

THE ECONOMIC VALUE OF PERITONEOSCOPY

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PERITONEOSCOPY, or the direct inspection of the abdominal cavity with an endoscopic instrument, is a diagnostic procedure known to clinicians since 1901. The most important contributions toward its development are found in Table I.

At the Memorial Hospital our chief interest in this endoscopic field has been in the determination or recognition of the inoperability of various intra-abdominal neoplasms. One can frequently appreciate the inoperability of some cancers by this examination, but, on the contrary, the resectability can never be ascertained with any degree of certainty. If this fact were universally known, the limitations of the instrument would be accepted and no extravagant claims for its use would be made. The recognition of metastases in the liver or carcinomatous implants on parietal or pelvic peritoneum, for example, would discourage any surgical attempt at removal of a gastric cancer. On the other hand, a cancer apparently confined to the stomach, as viewed through the peritoneoscope, may be definitely inoperable because of retroperitoneal involvement, infiltration around major blood vessels, etc. The diagnosis of cancer of the stomach and the majority of other intra-abdominal tumors has usually been established before peritoneoscopy is contemplated, so it is seldom employed for this purpose. The chief indication for its use, in our hands, is the attempted determination of inoperability, in borderline cases, when clinical evidence of such inoperability does not exist. With this point of view, one could not make the mistake of denying to any patient the opportunity for surgical relief or cure. If the criteria which determine inoperability are not fulfilled on peritoneoscopic study, a celiotomy immediately follows, and the tumor is then found to be resectable or inoperable. This discovery of inoperability should not be listed as a failure for peritoneoscopy, because it only confirms the well-recognized limitations and handicaps of the method.

This relatively safe minor procedure will often prevent useless exploratory celiotomies in patients who are poor surgical risks. The economic advantages to the patient, and to the hospital, will be discussed later in greater detail. Peritoneoscopy is generally indicated in the following conditions: Intra-abdominal tumors, particularly malignant tumors; cirrhosis of the liver; ascites of undetermined origin; tuberculous peritonitis; ectopic pregnancy; and lesions of the internal female genitals. The procedure is contraindicated in acute inflammatory conditions of the abdomen; advanced cardiac or pul-

monary diseases; and extensive peritoneal adhesions. The single death in this series occurred in a jaundiced patient; this fatality, from slow, hidden intra-peritoneal hemorrhage would not occur now, with the routine employment of prothrombin estimation and vitamin K therapy.

TECHNIC OF PERITONEOSCOPY

After preliminary sedation with morphine and scopolamine, the abdominal wall is prepared as for any celiotomy. In addition to sterile gowns and gloves, the operator, and his assistant, wear sterilized fiber masks and sterile

TABLE I
HISTORICAL DEVELOPMENT OF PERITONEOSCOPY

Name	Year	Contribution
1. Kelling	1910	"Kölloscope" — First demonstration made on a living dog. Used a cystoscope, and was the first to inflate the abdomen with air.
2. Jacobaeus	1910	"Laparoscopy" — Received recognition for the procedure. Was the first to apply pneumoperitoneum to roentgenologic diagnosis.
3. Bernheim	1911	The first American to attempt peritoneoscopy. Devised a proctoscope of one-half-inch bore which he inserted through a small incision in the epigastrium. Head mirror used for source of illumination. Used the term "organoscopy."
4. Nordentoeft	1912	Devised a "trochar-endoscope." Was the first to describe the endoscopic appearance of the female organs with the patient in the Trendelenburg position.
5. Nadeau and Kampmeier	1925	Published a complete description of the technic of endoscopy of the abdomen.
6. Ruddock	1937	Devised superior instrument. Outlined standard procedure. Introduced the term "peritoneoscopy."

spectacles. The operating room is completely darkened. A site for the introduction of the instrument is selected in the midline immediately below the umbilicus. The skin, subcutaneous tissues, fascia, muscle and peritoneal fat are infiltrated with one per cent novocaine. A vertical incision, not more than two centimeters in length, is made, and the tissues are retracted with narrow right-angle retractors until the posterior rectus sheath and peritoneum are exposed. A small blunt trochar is introduced into the peritoneal cavity and air is pumped in by means of an attached hand bulb. After a good-sized air space is secured (determined by abdominal tympany), a large trochar is inserted, the obturator removed, and the telescopic lens introduced. Examination of the peritoneal cavity including the visible organs and the serosal and parietal peritoneum is then undertaken. The pelvic cavity and its contents are best visualized by placement of the patient in the Trendelenburg position, whereas, the liver, gallbladder and stomach are best seen with the patient in the extreme opposite position, *i.e.*, with the superior half of the body elevated by 20 to 40 degrees (Fig. 1). Proper adjustment of shoulder braces and footboard facilitates this procedure. The peritoneoscope should be kept close to the parietal peritoneum and advanced always in a relatively horizontal direction in order to avoid injury to the viscera. The introduction of the Ruddock stomach tube with illuminated tip is of some help, as it aids the observer by transillumination of this organ. The peritoneum, fascia and skin are closed by the insertion of black silk sutures.

PERITONEOSCOPY

The lack of a modern Ruddock peritoneoscope does not constitute a bar to successful peritoneoscopy. The examination can be successfully accomplished with a child's esophagoscope or a cystoscope, as we occasionally did 10-15 years ago.

END-RESULTS OF PERITONEOSCOPY

Since January 1940, peritoneoscopy has been employed upon 80 patients at the Memorial Hospital. Of these, 26 had primary gastric cancers, 12 had

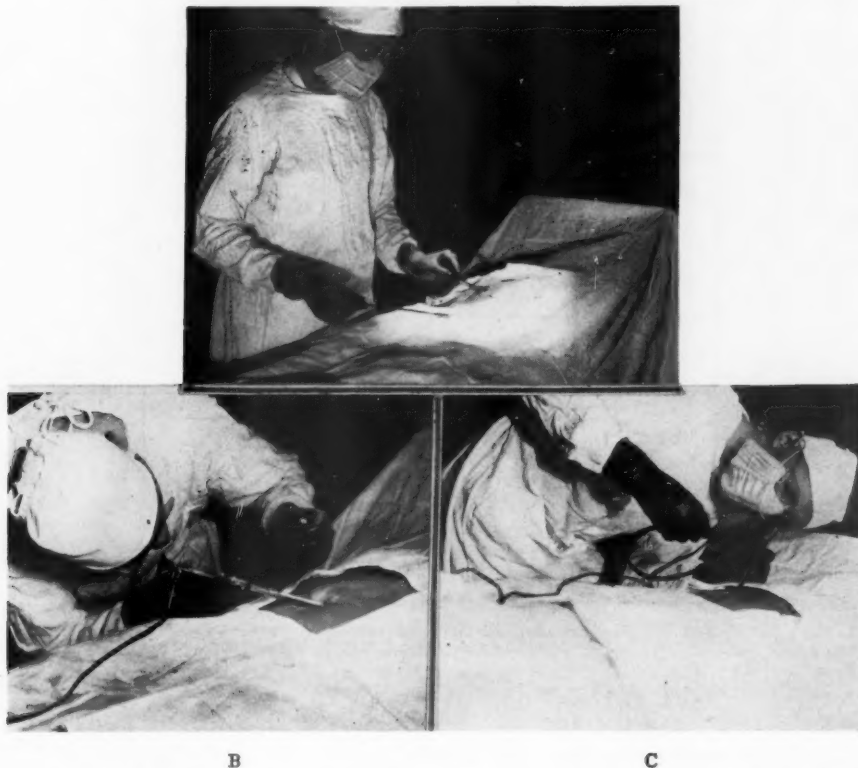


FIG. 1.—A. Preliminary introduction of trocar into peritoneal cavity. Note sterile face mask and glasses.
B. Examination of upper abdomen with the body of patient inclined, so as to elevate the upper half.
C. Examination of the lower abdomen with the patient in the Trendelenburg position.

cirrhosis of the liver, seven had neoplasms of the gallbladder or liver, and six patients with mammary cancer had peritoneoscopic visualization of their livers. The diagnoses in the remaining 29 cases (36.25 per cent) are found in Table II.

Of the 26 patients with carcinoma of the stomach, who were subjected to peritoneoscopy, the purpose of peritoneoscopy was satisfactorily fulfilled in 53.8 per cent (14 patients). In seven patients, metastatic cancer was found to involve the liver, parietal peritoneum, or both, and in this group a major operation was avoided. In seven other patients, whose gastric cancers were

at first thought to be of questionable or borderline resectability, the endoscopic findings did not contraindicate surgical exploration, which was undertaken and the cancers removed. In 46.1 per cent (12 patients) the procedure was of little value. In this group, it was demonstrated that resectability of the cancer cannot be forecast on peritoneoscopic inspection of the liver, peritoneum or abdominal viscera alone.

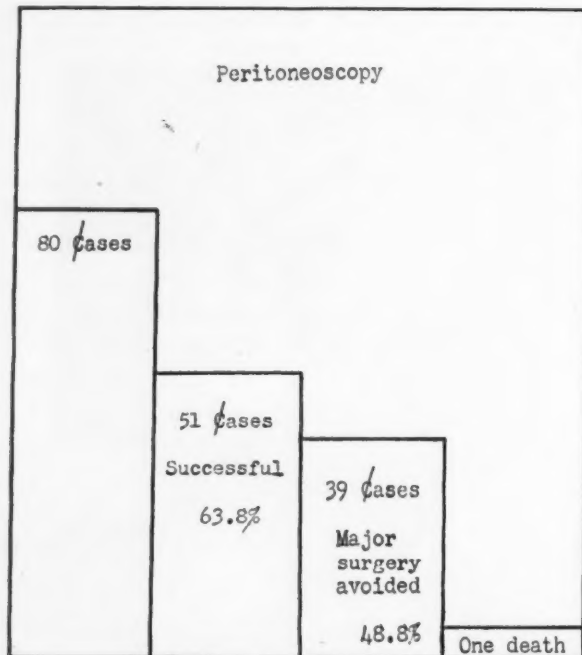


FIG. 2.—Demonstrating the value of peritoneoscopy as an aid or substitute for celiotomy.

Peritoneoscopy is of great value in the differential diagnosis between cirrhosis and malignant tumors involving the liver. In our group of 12 cases, exploratory celiotomy was avoided in nine, owing to the fact that the correct diagnosis was easily established on peritoneoscopy. Four patients with presumptively operable cancers of the breast had slight enlargement of their livers; on peritoneoscopy, three were declared inoperable because of hepatic metastases. The other patient subsequently had a radical mastectomy. Two other patients who had undergone radical mastectomy were found to have metastases in the liver.

In evaluating this diagnostic procedure, therefore, consideration should be given to (1) the possibility of avoidance of an unnecessary celiotomy; (2) the rate of operative mortality and morbidity of exploratory celiotomy, *versus* peritoneoscopy; and (3) the economic factor. In this series of cases, peritoneoscopy disclosed the disease to be so extensive that exploratory celiotomy was avoided in 39 patients, or 48.8 per cent (Table III and Fig. 2). The average duration of hospitalization of these patients was 48 hours. One death

PERITONEOSCOPY

TABLE II
CLASSIFICATION OF CASES

	Number	Per Cent
Total cases.....	80	100.00
Primary carcinoma of the stomach.....	26	32.50
Cirrhosis of the liver.....	12	15.00
Tumors of the liver and the gallbladder.....	7	8.75
Carcinoma of the breast (metastatic to the liver).....	6	7.50
General abdominal carcinomatosis (primary site unknown)....	3	3.75
Primary carcinoma of the ovary.....	3	3.75
Hepatoma of the liver.....	2	2.50
Carcinoma of the large bowel.....	2	2.50
Metastatic carcinoma to the liver (primary site unknown)....	2	2.50
Melanoma of the eye (metastatic to the liver).....	1	1.25
Chronic pericarditis, with ascites.....	1	1.25
Generalized melanoma.....	1	1.25
Carcinoma of the colon.....	1	1.25
Lymphatic leukemia, lymphosarcoma of the stomach.....	1	1.25
Carcinoma of the tongue (metastatic to the liver).....	1	1.25
Lymphosarcoma of the spleen.....	1	1.25
Cervical polypus and hepatomegaly.....	1	1.25
Carcinoma of the lung (metastatic to the liver).....	1	1.25
Primary carcinoma of the rectum.....	1	1.25
Postirradiation intestinal adhesions.....	1	1.25
Lymphosarcoma of the groin and liver.....	1	1.25
Carcinoma of the larynx, benign gastric ulcer.....	1	1.25
Carcinoma of the esophagus.....	1	1.25
Carcinoma of the kidney (metastatic to the liver).....	1	1.25
Carcinoma of the bladder.....	1	1.25
Carcinoma of the pancreas.....	1	1.25

TABLE III
END-RESULTS OF PERITONEOSCOPY

A. Complete Summary of 80 Cases

Procedure successful in 51 cases.....	63.8 per cent
Operation avoided in 39 cases.....	48.8 per cent
Procedure failed to prevent operation in 23 cases.....	28.8 per cent
Operation not undertaken because of other factors in five cases.....	6.3 per cent
Death followed peritoneoscopy in one case.....	1.3 per cent

B. Carcinoma of the Stomach — 26 Cases — 32.5 per cent

Procedure successful in 14 cases.....	53.8 per cent
Operation avoided in seven cases.....	26.9 per cent
No cause for inoperability discovered in seven cases.....	26.9 per cent
Procedure failed to prevent operation in 11 cases.....	42.3 per cent
Operation not undertaken because of other factors in one case.....	3.8 per cent

C. Cirrhosis of the Liver — 12 Cases — 15 per cent

Diagnosis made and operation avoided in nine cases.....	75 per cent
Diagnosis not made but findings at operation showed there was no indication to prevent operation in one case.....	8.3 per cent
Procedure failed to prevent operation in one case.....	8.3 per cent
One patient died.....	8.3 per cent

D. Tumors of the Liver and Gallbladder — 7 Cases — 8.75 per cent

Procedure prevented operation in five cases.....	71.4 per cent
Procedure failed in two cases because of adhesions from previous operations.....	28.6 per cent

E. Carcinoma of the Breast — 6 Cases — 7.5 per cent

Procedure successful in 100 per cent of the cases
Radical operation and further studies avoided in five cases
Operability determined in one case

F. Mixed Tumors — 29 Cases — 36.25 per cent

Procedure successful in 17 cases.....	58.6 per cent
Operation avoided in 13 cases.....	44.8 per cent
Operability determined in four cases.....	13.8 per cent
Procedure failed to prevent operation in seven cases.....	24.1 per cent
Operation not undertaken in five cases, but peritoneoscopy was not the deciding factor.....	17.2 per cent

occurred in the group of 80 patients, the result of intraperitoneal hemorrhage in a patient with cirrhosis of the liver and a low prothrombin level. No obvious source of bleeding could be found on postmortem examination. This single operative death may be contrasted, for example, with that for exploratory celiotomy for cancer, which is generally in the neighborhood of eight per cent.

The brief period of hospitalization is of economic significance to the patients. At the present time, the total minimum cost (exclusive of professional fees) to a patient occupying an inexpensive private room for two weeks is \$140. Add to this the routine charges of \$55 for anesthesia and the use of the operating room when a major operation, such as an exploratory celiotomy is performed, and the total amounts to \$195 without additional expenditures, such as nursing care, medicines and laboratory charges. This is in contrast to the sum of \$58.50, or the total expense for two days' hospitalization, including the operating room cost, when peritoneoscopy is undertaken on patients of similar financial status. For ward or clinic patients, a comparable financial saving occurs—\$86 minus \$15, the cost of exploratory celiotomy, and \$24, the cost of peritoneoscopy.

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SPONTANEOUS INTRA-ABDOMINAL HEMORRHAGE

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HEMORRHAGE within the abdomen and into the peritoneal cavity is not in itself uncommon. However, when we exclude bleeding of a genital origin in females, bleeding due to rupture of abdominal aneurysms and bleeding due to direct trauma, we find that the spontaneous rupture of a splanchnic vessel is very rare. It is this condition which has been termed "abdominal apoplexy" by some, with which this paper deals. To the best of my knowledge, only 26 instances in 25 patients have been reported since 1911. It is the purpose of this paper to report three additional cases which have been observed at Cleveland City Hospital during the past year.

It has been said that there is nothing pathognomonic in either the symptoms or the signs of this entity to permit certain preoperative diagnosis. Such has been our experience. However, after analysis of the previously reported cases, Cushman and Kilgore have described the syndrome and believe that it can be diagnosed with a certain degree of certainty. They state that as long as the hemorrhage is confined within the leaves of the mesentery that the pain is typically that of a dull, sickening type. The initial pain is usually sudden in onset, and persistent or gradually subsiding rather than colicky in nature. We would add that it becomes colicky if actual obstruction is present. It is usually accompanied, sooner or later, by vomiting. Neither does vomiting nor evacuation of the bowel relieve the pain. In 11 of the cases previously reported, the pain subsided only to recur in a few hours to several days. This obviously depends upon the site, amount and recurrence of the actual hemorrhage. When tension around the hematoma is released, sudden excruciating pain is experienced; this is followed rapidly by collapse and signs of shock if hemorrhage of significant amount occurs. This phase may be initiated by vomiting, by the use of purgatives or by mild physical activity, any of which may, in turn, reestablish bleeding.

A certain amount of leukocytosis is usually seen, and when the blood actually enters the peritoneal cavity this becomes even greater. The red blood count and hemoglobin determinations may be helpful, but these depend greatly upon the amount of bleeding and the state of hydration of the patient.

A point of more than academic interest is that 56 per cent of the reported cases had signs of arteriosclerosis and/or hypertension. The average age of the group was approximately 56. When carefully questioned, some gave the history of some physical activity when the pain was first noted, *e.g.*, carrying a heavy load or bumping into someone. The celiac axis was involved in 8 of the cases, the superior mesenteric and its branches in 13, and in three cases the origin of the bleeding was not found or stated. Of this

group, 19 patients were operated upon. Ligation of the bleeding point was carried out in seven, and no point of hemorrhage was isolated in 12. Five of the operated group (26 per cent) died. Only one case was diagnosed correctly and proven by operation.⁶ Two cases reported by Cushman and Kilgore, one of which is the only recurrent case on record, were not operated upon, and recovered. Roughly, one-third of the patients began with pain but did not go on to collapse; one-third after an indefinite period went into shock; rupture of the hematoma occurred so early in the remaining third of the cases that collapse was almost the initial symptom.

The cases which we report consist of three colored males ages 55, 43 and 55, respectively.

Case 1.—H. G., Negro, male, age 55, was admitted January 3, 1944, with a chief complaint of epigastric pain. This had come on suddenly about three hours before admission, while lifting a shovel full of ashes. It was sharp and very severe, there was a tendency for it to bore directly through to the back and though present continuously there were times when it became colicky and more severe. He had vomited twice before admission and once shortly thereafter. His last meal had been one hour before the onset of pain, and his last bowel movement had been on the preceding day. He had felt perfectly well until one day previously when slight anorexia was noted. His past history revealed that he had had a penile lesion at the age of 17 which had never been treated.

Physical Examination.—The patient was well-nourished and well-developed. Temperature 37.7° C.; pulse 114; respirations 20. Blood pressure 84/70. He was perspiring freely. General examination was essentially negative other than that relevant to the abdomen. The abdomen was markedly tender over a small area in the left epigastrium, with some tenderness in the left lower quadrant. Some spasm was also present in the left upper quadrant. Slight rebound tenderness was present throughout. No masses were felt and no borborygmi were heard. Liver dullness was present. On rectal examination, good tone was noted and there was no pelvic tenderness. Red blood cells 4,160,000; white blood cells 8,800. The urine contained one plus albumin, specific gravity 1.028. Roentgenograms of the abdomen were negative, and an upright film of the chest showed no free air under the diaphragm.

Continuous gastric suction was instituted. After giving him intravenous fluids, including plasma, his blood pressure rose to 124/72; pulse 130.

Operation.—Exploratory celiotomy was performed under procaine intraspinal anesthesia. A large number of clots and considerable free blood were found in the peritoneal cavity. An hematoma, the size of a grapefruit, was found near the hepatic flexure in the transverse mesocolon, the inferior leaf of which had a laceration about four inches long in it near its base. As much of the hematoma as possible was evacuated, along with the remaining blood in the peritoneal cavity. No definite bleeding point was seen. The laceration was then closed with continuous interlocking suture of No. 00 chromic catgut. The abdomen was closed by through-and-through No. 8 Deknatel sutures. Blood pressure at the end of the celiotomy had risen to 170/130.

Except for some vomiting on his 11th to 14th postoperative days, he made an uneventful recovery, and was discharged, January 28, 1944, after a negative G. I. series. His blood Kline was ++++ in both diagnostic and exclusion tests. His condition was good when recently seen in the out-patient department.

Case 2.—G. M., Negro, male, age 43, was admitted, January 13, 1944, with a history of generalized, vague abdominal discomfort of 48 hours' duration. Shortly after its onset he began vomiting and had continued to do so, being unable to retain food or liquids of any kind. He had had no bowel movements for three days, though he had taken several

laxatives since the onset of his present illness. The pain was more severe in the upper abdomen and right paraumbilical region and had not shifted in any direction since its onset. The past history was noncontributory.

On admission, his temperature was 38.8° C.; pulse 96; respirations 28; and blood pressure 150/120. The patient was well-developed and well-nourished. The skin was dry and warm. General examination was essentially negative other than that relevant to the abdomen. The abdomen was flat and no visible peristalsis was present. There was moderate tenderness in the right epigastrium and right paraumbilical region, the latter point being somewhat more tender. Rigidity of the right rectus muscle was present. No borborygni were heard. Red blood cells 4,800,000; white blood cells 13,600. The urine had a specific gravity of 1.035, and had 8 to 10 hyaline and granular casts and an occasional white blood cell and red blood cell in each high power field.

Because it was felt that he probably had high intestinal obstruction, a small amount of thin barium was given the patient and watched under fluoroscopy. It was impossible to fill the distal portion of the stomach. A plain film of the abdomen and a chest film were negative. Constant gastric suction was started and intravenous fluids, including plasma, were given. An exploratory celiotomy through a right rectus incision was then performed, under procaine intraspinal anesthesia. A large mass, about 10 x 5 cm. in diameter, was palpated within the "C" loop of the duodenum. Incision was made through the gastrocolic ligament and then through the peritoneum, behind which the hematoma was expressed as completely as possible. No bleeding point was found and the peritoneum and gastrocolic ligaments were closed. No freed blood was present in the peritoneal cavity. The abdomen was then closed, using chromic catgut in layers. He has been seen in the out-patient department on two occasions, and has had no recurrence of symptoms. His blood pressure was 170/94 and 145/100 at these times. Blood calcium, bleeding time and clotting time have been normal.

Case 3.—O. W., Negro, male, age 55, was admitted, April 10, 1943, with a chief complaint of heart trouble and abdominal pain. He had been treated elsewhere for about four months because of shortness of breath with marked dyspnea on exertion, orthopnea and ankle edema. He also had been told that he had high blood pressure. Three weeks before admission he became worse and had been confined to his bed; about three days previously he had first noted vague abdominal pain which was more pronounced in the epigastrium and right upper quadrant. There had been some associated vomiting, the nature of which was also rather vague. On the morning of admission he had had a "fainting spell" accompanied by profuse diaphoresis and weakness.

On admission, his temperature was 37.2° C.; pulse 108; respirations 28; and blood pressure 188/148. He was a well-developed but rather poorly nourished colored male, who was lying rather listlessly in bed and who was rather dyspneic. There was no cyanosis noted. His skin was warm and moist. The pupils reacted to light and accommodation, and fundoscopic examination revealed moderate sclerosis of the vessels with areas of degeneration and recent hemorrhages visible. The thyroid was not palpable. There was slight venous distention of the cervical veins. The lungs were clear to percussion and auscultation except for transient rales at each base. The left border of cardiac dullness was at about the nipple line. The cardiac rhythm was regular and no murmurs were heard. The peripheral vessels were tortuous and sclerotic. The abdomen was diffusely tender but this was more pronounced in the right upper quadrant. Only voluntary spasm was present. Each costovertebral angle was also tender. The liver was palpable one fingersbreadth below the right costal arch. A left hydrocele was present. The reflexes were generally hypoactive. Marked tenderness was present above the prostate. Red blood cells 3,800,000, hemoglobin 11 Gm.; white blood cells 30,000. The urine was loaded with white blood cells. The impression was hypertensive cardiovascular disease with arteriolar nephrosclerosis and pyelonephritis.

Following his evening meal on the day of admission he vomited and then immediately fainted, remaining unconscious for about two minutes. He perspired freely and was slightly euphoric. His pulse was very rapid, thready and irregular. Marked dyspnea was noted. He responded fairly well to 50 per cent glucose and aminophyllin but remained lethargic. A lumbar puncture was done; mechanics and pressure were normal and a cell count of 26 was noted. The blood urea nitrogen was 51.8, and creatinine was 4.8. Surgical consultation confirmed the impression of bilateral pyelonephritis and uremia. Genito-urinary and chest films were negative except for the evidence of cardiac enlargement.

After three days the abdominal signs had disappeared completely except for accurate point tenderness in the right upper quadrant. His white blood count was 9,400, and the urine had essentially cleared. Blood pressure remained at a somewhat higher level than that recorded on admission, the highest figure recorded being 245/142. Vital capacity was two liters.

Digitalization was started. The patient appeared to improve until 14 days after admission when abdominal cramping pains started. They became progressively more severe and were associated with nausea and vomiting. When seen in surgical consultation he had exquisite tenderness and spasm in the right upper quadrant with some spasm throughout the entire abdomen. Moderate rebound tenderness and distention were present. The impression at that time was an acute exacerbation of chronic cholecystitis. A plain film of the abdomen and a chest film failed to show any sign of perforated intra-abdominal hollow viscus; however, two shadows were seen which were interpreted as gallstones. Because of his hypertension, with moderate cardiac failure and uremia, he was considered a poor surgical risk. On the following three days his abdominal tenderness, spasm and distention were markedly improved, when suddenly, on his 18th hospital day, he became dyspneic; his pulse went up to 180, and blood pressure was 100/60. Other signs of shock were present. The abdomen was very distended and tenderness and spasm were now chiefly in the left upper quadrant. His pulse and blood pressure were unobtainable 30 minutes later, and he died one hour later, without any response to symptomatic therapy.

Autopsy was performed and the following diagnoses were made: (1) Organizing hematoma at head of pancreas, with rupture through mesocolon near hepatic flexure and hemorrhage into peritoneal cavity (3100 cc. of fluid, with a specific gravity of 1.024); (2) chronic cholecystitis, with cholelithiasis; (3) slight chronic pancreatitis; (4) marked bilateral pyelonephritis; (5) generalized arteriosclerosis; and (6) left inguinal hernia with hydrocele, bilateral.

Beneath the 5-cm. rent in the hepatic flexure was a hematoma, about 10 x 8 cm. in diameter. It did not involve the kidneys, the adrenals or any of the gastro-intestinal tract except the mesocolon and the "C" loop of the duodenum. The medial portion of the mass was in direct contact with, but definitely did not communicate with, the head of the pancreas. Exploration of the celiac and superior mesenteric vessels revealed no evidence of rupture or thrombosis. The walls of the bowel were intact. On the right border of this mass another mass, measuring 5 x 3 x 2.5 cm., was found. Its wall was 4 mm. thick and its contents gelatinous; this was interpreted as being an older hematoma.

DISCUSSION.—In selecting these three cases to report, and in reviewing the literature, every effort has been made to include only those which were truly spontaneous in origin. For this reason, one of the previously reported cases was omitted because of the circumstances; a deep epigastric vein had ruptured during labor. In our minds this could not be called spontaneous in origin. Another condition which may be associated with marked intra-

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abdominal hemorrhage is acute pancreatitis. Recently, a patient with this finding was operated upon at City Hospital but, because of the extensive necrosis in the pancreas, that case is not considered here. Although our third case was in the general region of the pancreas, it was the opinion of the pathologist that this hematoma did not communicate with that organ.

All three of these cases had arteriosclerosis, with associated hypertension that was quite definite; all were males. The average age incidence was approximately the same as for the previously reported cases, although the former group varied from the age of 27 to 80.

Each of our cases represents a different stage in this condition. The first was operated upon following rupture of the intramesenteric hematoma into the abdominal cavity; the second was operated upon before this perforation had occurred, but the hematoma was causing intestinal obstruction. The third case shows what course repeated intra-abdominal hemorrhage may pursue. In neither of our operated cases was an actual bleeding point found and ligated, but both recovered. An attempt was made to correlate the type and location of pain each had with the anatomic findings, but in most instances this has been unsatisfactory. For this reason we are hesitant about describing any "typical" syndrome.

SUMMARY

1. Three cases of spontaneous intra-abdominal hemorrhage have been reported; two of these cases were successfully operated upon; the third being diagnosed at autopsy.

2. An analysis of the 26 previously recorded cases has been discussed.

3. Even though this is a rare condition, we believe that it should be held in mind as an aid in diagnosis of obscure acute intra-abdominal pathology. It should be emphasized, however, that the symptoms and signs of abdominal apoplexy are dependent upon the site, the amount, and the rate of bleeding.

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COMPARATIVE STUDIES OF CANCEROUS VERSUS NONCANCEROUS BREASTS*

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II. ^AROLE OF SO-CALLED CHRONIC CYSTIC MASTITIS IN MAMMARY CARCINOGENESIS INFLUENCE OF CERTAIN HORMONES ON HUMAN BREAST STRUCTURE

WE DO NOT EMPLOY the term "chronic cystic mastitis" in the diagnosis of lesions of the breast, since it conveys no indication of the presence or absence of many characteristic histopathologic changes; moreover, it implies a common etiology for a variety of lesions, most of which are anything but basically inflammatory processes. The deficiencies of the term have been recognized by many writers, some of whom have proposed new designations not always without merit. This multiplication of terminology has been, perhaps, partly responsible for furthering the usage of the expression "chronic cystic mastitis," since it affords a means of escape from a more complicated nomenclature. At the present time no universal agreement exists as to the precise lesions that should be included under the term "chronic cystic mastitis." That these lesions are of multiple histologic type will be conceded by most observers, but when it comes to selecting the true representatives there is disagreement. Some authors seem to exclude nothing, but beyond this very liberal point of view the requirements become somewhat more strict. Our impression is that most writers are liberal. The term "chronic cystic mastitis" is so ingrained in the minds of some pathologists that this diagnosis of a locally excised portion of breast almost amounts to a surgicopathologic reflex. Such haphazard terminology leads to neglect of the actual histologic features present, and an accurate diagnosis demands an enumeration of actual lesions, even though it may enforce the employment of a rather complicated terminology. Even if a certain group of lesions is eventually accepted as component parts of "chronic cystic mastitis," it seems reasonable to list which of these are present when diagnosis is made in a given case. It is not assured that all of these lesions are of equal importance, and unless mentioned categorically, the determination of which constitute the important ones will continue to be delayed. There is further need for speaking in specific terms, since etiologic factors are still in dispute, and every assistance which might contribute to this problem should be given. Clinical correlation would be facilitated by more definite designation of pathologic lesions.

Much of the confusion that exists in the literature on the subject under discussion stems from the following sources: Too little regard has been given structural features that depend directly upon age. Reports on relatively scanty material are all too frequent. Very little attention has been

* Continued from ANNALS OF SURGERY, January, 1945.

directed to periodic changes related to the menstrual cycle, and, hence, physiologic alterations have been interpreted as pathologic. Observations of hormonal influences on the mammary glands of lower animals have been too freely transposed to the human female breast. Many studies have been made by reviewing old material which was not prepared with any particular objective; this applies particularly to cancer-containing breasts where little if any stress was laid on the noncancerous portion of the breast. Serial sections have seldom been used to trace the origin and distribution of certain abnormal proliferations. Many conclusions have been made on a statistical basis alone with no effort to establish a supportive morphologic relationship based on histologic traceability. Gross observations on fixed material commonly lead to certain errors that are avoided in fresh dissections. There has been a tendency to draw conclusions as to genesis from observations of lesions far too advanced to permit interpretation of origin. Failure to recognize certain changes as postmortem or post-excisional, as the case may be, causes misinterpretation. This is absolutely unavoidable if large sections of tissue are fixed in bulk.

Any point of view that one chooses to take concerning the causal relation of so-called chronic cystic mastitis to mammary cancer can be abundantly supported from the literature. The coincidental occurrence of cancer and so-called chronic cystic mastitis is variously reported. The most extreme figure is 100 per cent, found by MacCarty and Mensing⁸ in a series of 967 mammary carcinomas. The explanation for this high figure is at once apparent by quoting the histologic criteria employed by them: "By chronic mastitis is meant the presence of one or more of the following conditions: Fibrosis, hyalinized fibrosis, lymphocytic infiltration, distortion, partial or complete destruction of the glandular groups, obliteration or dilatation of acinic lumina, atrophy, hypertrophy or hyperplasia of the parenchyma." A histologic net of this sort would, indeed, trap the wariest breast. A contrasting report was made by Bloodgood⁹ in 1921 (page 541 of the article): "It is important to record that the histologic pictures shown in Figures 33 through 85, and 90 and 91, have never been observed in the breast of a patient whose glands showed metastasis, or who had definite cancer." When one reviews Bloodgood's photomicrographs, which encompass nearly every type of lesion commonly present in surgical specimens of breast, cancerous or noncancerous, he wonders what sort of study could have enabled the comment, and he must conclude that in Bloodgood's cases of cancer, little or no attention was paid to noncancerous areas. Between the two extremes just mentioned, almost any percentage of coexistence can be found. Charteris¹⁰ reported evidence of "chronic cystic mastitis" in 85 per cent of 48 radical mastectomies for cancer. The coexistence recorded by Rodman¹¹ was 15.5 per cent. In a long monograph Semb¹² used the terms "fibro-adenomatosis simplex (microcystica)" and "fibro-adenomatosis cystica." In 140 cases of cancer he found "fibro-adenomatosis" in 80 per cent, 40 per cent being of the "simplex (microcystica)" type and 40 per cent being of the "cystica"

type. (Note that Semb's "cystica" group includes papillary lesions.) Semb defined his histologic criteria accurately, but it is noteworthy that on page 275 he acknowledges that his determinations were made without regard to menstrual changes. Logie¹³ used the term "cystic mastopathy" and described the morphologic complex of lesions that it included. In 118 cancerous breasts, 67 (56.7 per cent) had evidence of mastopathia cystica. Many other reports could be cited but the preceding should suffice to illustrate the statistical disagreement concerning the coexistence of cancer and so-called chronic cystic mastitis. It is to be noted that most writers base their diagnosis of "chronic cystic mastitis" or a term of their own selection, on the presence of at least one of a varying group of histologic findings. Others make no mention as to whether a single lesion or multiple ones are required.

Suppose the presence of one or more of the following *pot-pourri* of lesions is adopted as being diagnostic of so-called chronic cystic mastitis:

TABLE XXI

- | | |
|-----------------------------------|-----------------------------------|
| 1. Cyst(s) | 7. Periductal mastitis |
| 2. Duct papillomatosis | 8. Fat necrosis |
| 3. Blunt duct adenosis | 9. Hyperplasia of duct epithelium |
| 4. Sclerosing adenosis | 10. Fibro-adenoma |
| 5. Apocrine epithelium | 11. Tendency to fibro-adenoma |
| 6. Stasis and distention of ducts | (fibro-adenomatoid mastopathy) |

Then, the 300 cases of mammary carcinoma studied here show the accompaniment of so-called chronic cystic mastitis in 83 per cent, while the incidence in the 200 noncancerous cases is 90 per cent. Each of the above lesions has been rather closely defined in earlier pages of this paper and each has easily recognized histologic characters. We have avoided including doubtful findings such as "fibrosis," "hyalinized connective tissue," "cellular connective tissue," "lymphocytic infiltration," "desquamation," "atrophy," "epithelial hyperplasia," and other similar terms. It is easy to see that with complete laxity in selection of criteria and inclusion of changes due to age and the menstrual cycle, the incidence would reach or approach 100 per cent for both cancerous and noncancerous cases.

The change designated as "hyperplasia of duct epithelium" may not constitute in every instance a definite pathologic finding, for it is not always easy to be certain of what constitutes the uppermost levels of normal, or whether apparent epithelial hyperplasia is in reality a chance tangential section of a fold in a duct, as demonstrated by Ingleby.¹⁴ In preceding sections evidence has been presented to show that fibro-adenoma and "tendency to fibro-adenoma" do not tend to occur together with other proliferative lesions. If these three members are eliminated from the tabulations and only the first eight are included, the following figures result: The incidence of so-called chronic cystic mastitis becomes 74 per cent for the cancer cases, and 76 per cent for the noncancer cases.

Earlier in this paper inference was made that the lesion complex of "stasis and distention of ducts," "periductal mastitis" and "fat necrosis" was not primarily related to a certain group of proliferative and cystic

lesions. It was stated that this nonproliferative triad might occur independently of the proliferative group, *i.e.*, in the absence of these lesions, or that it might occur in unison with this group. In the latter instance, however, the only morphologic relationship appeared to be in those cases where the periductal mastitis, *etc.*, seemed either incidental or secondary to anatomic obstruction. The nonproliferative triad did not furnish an anatomic source of origin for the development of cysts, papillomas, blunt duct adenosis, apocrine epithelium or sclerosing adenosis. If, then, in addition to the three lesions already eliminated from the initial group of 11 lesions, we omit stasis and distention of ducts, periductal mastitis and fat necrosis, there is a residue of the first five lesions listed in Table XXI whose characters may be summarized as "cystic and proliferative." (We have not included a probably related lesion, "primary lobule alteration," but this omission causes no appreciable difference in either the absolute or comparative determinations).

If we use the presence of at least one of the cystic or proliferative lesions as a standard for the diagnosis of so-called chronic cystic mastitis, this condition is found in 59 per cent of the 300 cancerous breasts, and in 65 per cent of the 200 noncancerous breasts. If multiplicity of lesions is made a requirement, the figures fall rapidly. When two or more lesions are required, the coexistence is 35 per cent in the cancer series, and the frequency is 43 per cent in the noncancer series. If three lesions are required, the corresponding figures are 17 per cent and 25 per cent respectively. These determinations are for the two classes of cases taken as a whole, and since the cancerous breasts average 49.5 years in age and the noncancerous ones 39 years, it is necessary to compare the incidence of the group of cystic and proliferative lesions by decades. This is given in Table XXII.

TABLE XXII
FREQUENCY OF CYSTIC AND PROLIFERATIVE LESIONS BY DECADES

Decade	Cancer Cases		Noncancer Cases	
	If One Lesion is Required	If More than One Lesion is Required	If One Lesion is Required	If More than One Lesion is Required
30-40.....	58%	37%	60%	40%
40-50.....	63%	47%	82%	60%
50-60.....	50%	15%	57%	30%

The immediately preceding figures, in general, show somewhat similar trends in the occurrence of these cystic and proliferative lesions in various age-groups whether the breast is or is not cancerous. Throughout, there is slight to moderate numerical preponderance in favor of the noncancerous breasts. Perhaps there is a greater actual preponderance in the noncancerous breasts than revealed by this study. It must be emphasized again that the determinations made in the noncancerous series are based almost exclusively on local excisions, and hence the entire breast cannot be represented. At the same time, however, it seems reasonable that these local excisions represent the most altered portion of the organ.

Various interpretations can be made from Table XXII. If one wished to discount (on statistical grounds) the influence of these five lesions on

the genesis of mammary cancer, he could state that they are somewhat more common in noncancerous breasts than cancerous ones, and that in women 50-60 years of age multiplicity of these lesions is twice as common in breasts free from cancer. On the other hand, it could be argued that the cystic and proliferative lesions are most commonly encountered in the ages 40-50, and that this decade produces more mammary cancers than any other. Or, one could consider the two conditions independent, but with certain temporal relationships and divergences which depend on the natural history of the two disease processes.

The references to other writers and the tabulations shown here should sufficiently demonstrate that the concomitant occurrence of cancer and so-called chronic cystic mastitis will vary statistically according to selection of lesions.

We have previously enumerated five lesions that can be described collectively as "cystic and proliferative." Their tendency to coexist has been emphasized and recorded in preceding tables. Certain morphologic interrelationships have been traced in former sections, while lack of morphologic relation to other stated lesions has been shown.

We have been unable to detect local factors in the breast that can be interpreted as causal. This statement is based principally upon study and observation of lesions in their earliest phases of development. The absence of detectable local factors and the anatomic and age distribution of these lesions suggest that they may represent a metabolic disturbance; and with the established cyclic histologic changes referable to the follicular hormone and the corpus luteum hormone, it is reasonable to suspect that imbalance between these metabolic agents may be etiologic. This viewpoint has been taken by Goormatigh and Amerlinck.¹⁵ Their conclusions were based on the study of changes produced in the mouse breast after injection of folliculin for varying periods of time. In the alterations produced it was their opinion that the major rôle was played by the corpus luteum hormone, the effects of which were prolonged by the administration of folliculin. While one must admit some resemblance in the changes reported to the disease in the human female breast, some features are lacking. No real proof of true cyst formation is offered, and to speak of a dilated duct as "cystic" may be misleading. Suffice it to say that Goormatigh and Amerlinck conceded the parallelism of the mouse and human lesions to be "*quasicomplet*." Lewis and Geschickter¹⁶ support the hormonal theory of etiology. They speak of two types of chronic cystic mastitis. In one of these, cysts predominate, and these they term "cystic disease." In the other type epithelial hyperplasia predominates, and this they term "adenosis." These writers refer cystic disease to the effects of theelin and adenosis to the effects of progestin. We are unable to dissociate our material so sharply into two such categories as have Lewis and Geschickter, since the cystic and the proliferative lesions have been shown repeatedly in our tabulated results to show a marked tendency to coexist. Lewis' and Geschickter's classi-

fication will fit some extreme anatomic forms of the disease under discussion, but it deals principally with accented features and does not fit the majority of cases. Lesions produced in rats by Geschickter and Byrnes¹⁷ after treatment with various estrogenic substances have some features in common with the human form of "chronic cystic mastitis." Burrows¹⁸ injected male mice with estrin and produced changes which he considered representative of chronic cystic mastitis. Careful survey of his text and examination of the photomicrographs show some resemblance to the human disease, but this seems forced, and interpretation must depend as much upon one's attitude as upon the lesions produced. As in Goormatigh and Amerlinck's work, no definite evidence of having produced clearly isolated cystic structures is given. The cystic and proliferative lesions produced in rats by Eisen¹⁹ with crystalline estrogen represent a rather satisfactory counterpart of those found in "chronic cystic mastitis" of the human female. Taylor and Waltman²⁰ failed to reproduce in mice treated with estrogen in oil a lesion-complex comparable to "chronic cystic mastitis" of humans. Greene²¹ has made interesting observations on a spontaneous familial disease of the rabbit breast in which the lesions closely simulate cystic and proliferative lesions of the human female. He regarded the observed changes as comparable to those found in animals after long continued administration of estrogenic substances.

All of the foregoing work briefly reviewed has a common defect, namely, that conclusions depend on the findings in rodent breasts. If one adopts the point of view that the lesions produced are equivalent to those in the human breast, is the hormonal basis proved for the human disease? Or, if one adopts the point of view that the lesions are not equivalent to those in humans, does it disprove a hormonal basis? It may well be that the physiologic gap between the two species is too wide for mutual transposition of morphologic observations. So far as we have been able to ascertain, there has not been any reasonably adequate histologic study of the human female breast under known conditions of hyperestrinism. Accordingly, no one can point to any group of pathologic lesions in the breast and maintain with certainty that they are due to this influence as, for instance, one may do in glandular and cystic hyperplasia of the endometrium. Adequate histologic data on breast lesions occurring under excessive administration of the corpus luteum hormone in women are also lacking. Normal cyclic changes and the changes seen in early pregnancy can be confidently related to specific hormonal influences, but abnormal histologic patterns at the present time must logically remain in doubtful status pending further investigation.

The statistical frequency of the coexistence of so-called chronic cystic mastitis and mammary cancer has engaged more attention perhaps than is deserved. Those who find in their studies a high rate of coexistence uniformly place more importance upon this finding than those who report a much lower coexistence. In our opinion a better proof of causal relationship depends upon showing a direct anatomic association rather than a mere statistical one. In other words, it must be demonstrated anatomically

that the lesions of so-called chronic cystic mastitis furnish the actual focal starting point or points for at least a certain number of mammary cancers. Though the most direct approach, this is at the same time the most difficult to achieve. This difficulty lies in the fact that mammary cancer, like nearly every other form of cancer, almost always is a far advanced process when it is first observed either clinically or microscopically. One is reduced to a minute group of chance findings in local excisions for supposedly benign conditions; or these may be added to in small measure by microscopic study of the macroscopically noncancerous portions of breasts that contain cancer. By so doing an occasional breast yields sections that show convincing transition lesions or foci that fulfill the criteria for true noninfiltrating cancer. These foci should have no continuity with an infiltrating tumor. Such examples as this in our own material are too few for us to make any estimate of how frequently cancer of the breast may begin in the various lesions that are part of the lesion complex, "chronic cystic mastitis." Though unable to give precise figures we can confidently say that we have seen cancer begin in duct papillomatosis, solitary and multiple, cyst, apocrine epithelium and blunt duct adenosis. This has been more fully commented on in other sections. Over a long period of years, a bulky material tediously studied may produce enough very early cancers to make possible a fuller analysis.

To date, the most practical and useful approach to the problem of "chronic cystic mastitis" and cancer has been the clinical follow-up method. Greenough and Simmons²² followed for from one to 17 years a group of 83 women who had local surgical excisions for cystic disease. In 4.8 per cent of these, carcinoma of the breast subsequently developed. One should bear in mind in this connection that in 1914 some histologic diagnoses of carcinoma were made on lesions that would not be regarded at the present time as cancer. In Johnson's²³ 101 cases of cystic disease, 61 were followed for one to 20 years and no carcinomas developed. Bloodgood,²⁴ in 1932, gave the follow-up record of a group of 350 cases of chronic cystic mastitis that had been operated upon prior to 1921.⁹ Not one of these cases had developed evidence of mammary carcinoma. It should be noted, however, that the whole breast had been removed in 61.5 per cent, leaving but a small group of suitable cases. Similar results were reported several years later by Lewis and Geschickter.²⁵ Of 271 cases of "adenosis" followed more than five years, two had died with breast cancer, and of 252 cases of "cystic disease" followed more than five years, one had died from breast cancer. It is not clear how many of these cases had operations, but apparently most of them had simple excisions. No statement is given concerning any patients who might have been living with breast cancer or upon whom a successful operation for breast cancer had been performed. Klingenstein²⁶ reported the subsequent development of carcinoma after local excision in two patients of 54 who were followed for two to 11 years. Campbell²⁷ reported his follow-up records of 290 cases. He grouped these into "simple cystic disease" and "adenocystic disease." Of 190 cases of simple cystic disease treated by local excision, 62

per cent were followed five or more years, and in only one did breast cancer develop. Of 43 cases of adenocystic disease, 52 per cent were followed five or more years, and in none did breast cancer develop. There were 57 cases treated by simple mastectomy. Of these 62 per cent were followed five or more years and one case developed cancer in the remaining breast.

One of the most recent and extensive follow-up studies is that of Warren,²⁸ notable in that much effort was made to place his conclusions on a sound statistical basis. He used the Massachusetts statistics for the death rate for mammary cancer among females, and estimated that the annual attack rate was twice the death rate. In addition, the expected annual incidence of mammary cancer in the general population was calculated for each decade. Warren pooled cases from two sources, Toronto and Boston. There were 602 cases from Toronto, 419 of which were followed five years or more. Of 900 Boston cases in which follow-up was attempted, this was successful in 604. In these the follow-up ranged from five to 21 years. In these 1206 cases, mammary cancer later was found in 42. According to Warren, the number of cancers expected to develop in a group of this size in the general population is 13.16. In the 1206 cases, 301 were designated by Warren as "chronic mastitis" and 743 as "chronic cystic mastitis." In these two combined groups 35 cancers developed. Twenty-five of these cancers were in the Boston material, as opposed to an expected number of 6.6. When calculations were made for age-group rates, the author concluded that "the breast cancer attack rate for women with chronic mastitis and related lesions in the age-group of 30-49 years is 11.7 times the rate for the Massachusetts female population; in the group over 50 years of age, 2.5 times as great; in the entire group, 4.5 times as great." It is stated by Warren that there is no way of knowing how many women in the general population who develop chronic mastitis come under observation, but he *assumes* (italics ours) that the proportion seeking medical attention is large. In other words, he implies a low incidence of chronic cystic mastitis in the population at large. In this connection the work of Keynes²⁹ deserves attention. This investigator removed one breast from 116 consecutive autopsies on female patients and made careful gross and microscopic examinations. Fifty-nine of the 116 breasts showed lesions of chronic mastitis. Keynes defined chronic mastitis as "manifested by dilatation of ducts and acini, accumulation in them of the products of epithelial activity, infiltration with lymphocytes, fibrosis, and epithelial changes." These designations are very general and make a high rate of occurrence almost unavoidable. It is recalled that MacCarty and Mensing, on the basis of similar criteria, reported an incidence of 100 per cent in a large series of cancer-containing breasts. Our own examination of 54 breasts from the population at large indicates that this source of material presents a much lower incidence and degree of so-called chronic cystic mastitis than the cancerous or noncancerous surgical breast.

The reasons for the varying reports on the frequency of mammary cancer

after chronic cystic mastitis are not clear. The character of the follow-up may be partly responsible. One undesirable feature is that most of these follow-up studies are incomplete, inasmuch, as only half, or a little more than half, of the total of all cases are successfully traced. The importance of the length of the follow-up period has been stressed by Warren as well as the age of the patient when she came under observation. A further omission from nearly all reports is a statement relative to whether or not the subsequent cancer developed in the same breast treated by local excision or the opposite one. Another common omission is in failing to indicate how long an interval elapsed between the local excision and the clinical recognition of cancer.

Statistical follow-up studies have so far not produced conclusive evidence that any specific lesion or lesions which are a part of so-called chronic cystic mastitis are particularly apt to be followed by cancer. Perhaps this would be possible if enough material could be followed, but this would require a follow-up group of several thousand cases, an endeavor of discouraging magnitude. Hence, available follow-up studies are, in essence, determinations of how frequently mammary cancer developed following local surgical excisions for benign, nonsuppurative lesions of assorted types. We, ourselves, have no such follow-up records to report, but we have some data that may be regarded as a follow-up in reverse. This has been done by checking over the series of 300 mammary cancers to determine how many of these cases had previous local excisions for nonsuppurative benign lesions. In so doing, 12 (4 per cent) such cases were found and are tabulated in Table XXIII. Extending our observations to a larger number of cases, it was ascertained from the records of 1200 cases of operable carcinoma of the breast that 29 (2.4 per cent) had previously had a local excision of breast for a noncancerous, nonsuppurative lesion. For control purposes the history of previous breast surgery in 1200 cases of cancer in other locations was investigated. These cases comprised an equivalent age-group and included cancer of the skin of the head and neck region, the uterine corpus and cervix. In these 1200 cases of nonmammary carcinoma only 13 (1.08 per cent) had histories of previous local surgical excisions of breast. Of further interest, is the fact that 29 of the 1200 cases of carcinoma of the breast had already, at time of admission, had the opposite breast removed for carcinoma. In the 1200 cases of nonmammary cancer, only eight had previously had a radical mastectomy for carcinoma. Since cases of cancer of the breast have had approximately two and one-half times the number of previous local breast operations than have had cases of cancer in other locations, there seems to be a positive relationship between previous breast abnormality and the later development of cancer in that organ. This, in some measure, implicates "chronic cystic mastitis," since the lesions of this complex are so numerous in the local excisions. In passing, it is pointed out that the figures just given emphasize the tendency of mammary cancer to be a bilateral disease. This has been attested to in the past by Kilgore,³⁰ and Davis.³¹

TABLE XXIII

Age at Time of Radical Mastectomy for Cancer	Age at Time of Local Excision	Cases in which Cancer Developed on Same Side of Local Excision	Cases in which Cancer Developed in Opposite Breast
55	41	Yes	
55	52		Yes
49	47	Yes	
44	34		Yes
45	33	Yes	
47	43	Yes	
47	18	Yes*	Yes
49	49	Yes	
43	29	Yes	
61	44		Yes
65	39	Yes	
40	33	Yes*	Yes
Total		9	5

* Bilateral local excisions in patients who later developed at different dates cancer of each breast.

Table XXIII shows clearly that follow-up studies of five-year and even ten-year periods fail to discover many of the cancers that develop after local excision, and, thus, Warren's²⁸ stress on the importance of length of follow-up is repeated. In Table XXIII a ten-year follow-up period would have failed to show the development of seven of the 12 cancers, giving a percentage of 1.7 for later cancer development as opposed to the true figure of 4 per cent. We get the impression that these latter figures represent possible maximums and minimums, and give some insight as to why various follow-up reports of later cancer development are apt to vary in about this range.

The 12 cases in Table XXIII are far too few to allow any conclusion as to whether or not any specific lesion present in the local excision was frequent enough to suggest that it was of definite precancerous nature, *i.e.*, in a statistical sense. One finding, however, is of particular interest. Of the 12 cancer cases that had previous local excisions, the cancer developed in the opposite breast in three instances, and in two other cases bilateral local excisions were performed. These facts must be borne in mind when one weighs prophylactic simple mastectomy as a therapeutic procedure in so-called chronic cystic mastitis. In these 12 cases where cancer developed some time after local surgical excisions, there were five instances in which it was anybody's guess as to which breast should have been removed "prophylactically." On this basis, if any prophylactic surgical procedures are employed, they must be bilateral simple mastectomies, or a large portion of the prophylaxis will be lost, since one cannot predict which breast will be the site of cancer at a later date. The present authors by no means favor either unilateral or bilateral prophylactic simple mastectomy as a standard form of treatment. Part of the reason for this point of view has just been discussed. Furthermore, if a program of "prophylactic" breast surgery were undertaken at the Memorial Hospital alone, it would impose the non-radical removal of slightly more than 1000 breasts annually. On the basis of published estimates already quoted, one year of this aggressive surgery would theoretically prevent from 5 to 20 cancers. Patients would scarcely

elect such a procedure, and were it known that it was contemplated, it is likely that many otherwise willing women would be frightened away from examining physicians, and allow their cancers to grow in private. It is our belief that women who have had a local excision for a nonsuppurative, nonmalignant breast lesion should be examined at least twice yearly for a prolonged period of years, since observations made in this study indicate that these individuals are more subject to mammary cancer than other groups. No one debates the desirability of clinical follow-up examinations of women who have had a radical mastectomy for mammary cancer, and certainly a leading reason for this is to observe the opposite breast; the chance of cure in recurrent or metastatic mammary carcinoma after radical mastectomy is so small as to minimize the practical importance of such a finding, but this is not so when a second primary cancer is found in the opposite breast. In the 300 mammary cancers studied here, 14, or 4.7 per cent, had already had one breast removed for cancer, and it is certain that others will develop cancer in the opposite breast. These determinations indicate that if one advises prophylactic mastectomies in "chronic cystic mastitis," he must, likewise, if he is logical, demand prophylactic removal of the opposite breast in any case having a radical mastectomy for cancer. From the reports of others the impression is gained that simple mastectomy for noncancerous breast lesions is performed in other clinics much more commonly than at Memorial Hospital, where this procedure is undertaken in less than 2 per cent of noncancerous cases. The rationale of simple mastectomy in "chronic cystic mastitis," so far as we can ascertain, has not been clearly demonstrated. The performance of this operation for "chronic cystic mastitis" should be discarded until specific lesions are proved beyond doubt to be followed by cancer in a sufficiently high percentage of cases to warrant the procedure. Since in our series of 300 radical amputations for breast cancer, 14 of the patients had already had the opposite breast removed for cancer, the following statement is suggested: The one most common "precancerous" lesion of the left breast is a cancer of the right breast and *vice versa*.

Present data are not sufficient to determine with exactness the importance of so-called chronic cystic mastitis in the over all development of carcinoma of the breast. Morphologic tracing of early phases of mammary cancer implicates the lesions of this complex in exceptional cases, and the soundest statistical studies point to some positive relationship. Until more fundamental knowledge of etiologic factors in both diseases is known, the extent of the relationship cannot be stated.

X—HISTOLOGIC FINDINGS IN BREASTS AFTER ADMINISTRATION OF ESTROGENIC SUBSTANCE

Exhaustive studies have been made of the influence of estrogens on the rodent breast. A much smaller number has dealt with effects in other species including lower primates. Some of these have been referred to in previous sections, but a full survey is not possible in this communication. In reviewing many past communications, however, one is impressed by the extreme

variability in response of the mammary gland. Many potentialities exist and are modified by such influences as species, strain, age, amount and duration of hormone administration, individual susceptibility and the type of estrogen employed. It is thought by many that the action of estrogens on the mammary gland centers primarily on the duct system and that progesterone acts on the lobules. Not controverting this general belief but illustrating the futility of set rules in mammary gland response are observations of Lewis and Turner,³² who found abundant lobule growth and alveolar secretion in a virgin female guinea-pig that received 0.25 mg. of diethylstilbestrol for 20 days. In a female ovariectomized monkey, Gardner and Van Wagenen³³ found extensive development of mammary lobules after 136,000 international units of hydroxyestrin benzoate, given over a space of 21.5 weeks in weekly fractions of 4000-8000 international units. These authors did not regard the change induced as comparable to a lactating breast, but inspection of the published photomicrograph reveals structure certainly consistent with late gestational hyperplasia. It is stated³³ that, in the rabbit, complete lobule development requires combined action of estrogen and progesterone. Specific reference to the foregoing is made here, since in our Case 10, that follows, we observed in the breast of a stilbestrol-treated postmenopausal woman widespread lobule formation, indistinguishable by us from the lobule pattern of lactating breast. The explanation of structural changes in breasts of the human female based on finding analogies in lower vertebrates must be treated with prudence, even though these analogies are gathering force.

The problem of whether or not estrogenic substances constitute a possible causative agent in the formation of mammary carcinoma in humans has been much talked of but little written upon. We have been able to discover three papers^{34, 35, 36} dealing with cases of breast cancer that were recognized during or shortly after estrogenic treatment. The very paucity of such recorded cases is rather indicative of a trivial rôle, since usage of estrogens has been widespread for a number of years. In the nine estrogen-treated cases that follow herein, five had carcinoma and in one of these patients the disease was bilateral. At the present time, we prefer not to enter into a critical discussion of the merits of these and the three cases already recorded. Not until more cases are available can a competent analysis be made.

One major reason for not attempting analysis of this problem is the lack of accurate basic knowledge of the structure of the human female breast following treatment with estrogenic hormones. Present descriptions are few. Haagensen and Auchincloss³⁵ examined the breast tissue in four cases after estrogen treatment. From three of these there were adequate amounts of tissue. One case showed only dilatation of ducts. In the other two there was "histologic evidence of marked stimulation of epithelium of the breast. The gland fields were large and numerous. There were areas in which small ducts multiplied to give the picture of adenosis. There were many dilated ducts. Some formed small cysts filled with amorphous debris. Others were partly, or entirely, filled with proliferating epithelium. The changes re-

sembled, in a general way, histologic changes observed in the mammary gland of mice after treatment with estrogens." In a case treated with theelin, Friedman, Finkler and Antopol³⁷ spoke of "moderate proliferation of duct buds." Hoffman³⁸ studied breast biopsies in two cases before and after administration of Progynon B. The histologic descriptions and photomicrographs in these cases alluded to the production of "characteristic alterations" in the posttherapy sections. Since the nature of "characteristic" breast alterations due to estrogenic influence is still a lingering problem with the present authors, we were unable to assimilate these conclusions. Geschickter⁶ makes brief mention of having studied breast biopsies from five women who had received from 25,000 to 100,000 international units of estrone for one to two months. He refers to "extension of the ducts, increase in the number of their lining cells and proliferation of periductal stroma." That author believed that these biopsies duplicated the appearance of an adolescent breast.

The cases reported below have some points of more than passing interest, but, in advance, it is stressed that we believe they offer little that carries beyond the range of speculation.

CASE REPORTS

Case 1.—L. S., age 41. Patient had a surgical menopause in 1938. Beginning in February, 1941, on account of menopausal symptoms, she received injections of theelin, 10,000 international units at weekly intervals. This therapy continued for several months and then there was a rest interval of six months. Following this the injections were resumed at the same rate and in the same amount as formerly, and these injections were continued until February, 1943.

In June, 1942, she noticed pain and a small area of swelling in her left breast. These symptoms disappeared in a few months, but in January, 1943, she became aware of a painless lump in her left breast.

When examined, February 24, 1943, the right breast was described as normal. In the 3 o'clock axis of the left breast, 10 cm. from the nipple, was a rather well-defined area of thickening about 2 cm. in diameter. This was freely movable, not attached to skin and thought clinically to be a fibro-adenoma.

On February 25, 1943, local excision of the above mentioned area in the left breast was undertaken.

Gross Examination.—Specimen measured 6 cm. in greatest diameter, and, on section, was composed principally of fat in which there were broad fibrous bands of breast tissue which contained no localized tumor, cyst or papillary lesion.

Microscopic Examination.—Duct system not remarkable. Lobules moderately numerous. In general, the acini are few in number and quite small. In other areas, however, they are somewhat more numerous, of larger dimension, and show graded transitional stages of apocrine metaplasia. Mitoses not present. Many acini are collapsed but others have patent lumina and contain nongranular material which stains bright pink to grayish-blue. Hyaline membranes not seen about acini. Duct papillomatosis, blunt duct adenosis, sclerosing adenosis not present.

COMMENT.—None of the above findings may be considered unusual in a breast five years beyond the menopause, with the possible exception that more lobular integrity was present than in the average case this far beyond the menopause. Transition phases in apocrine metaplasia will bear mention.

Case 2.—J. C., age 47. This patient's menopause occurred in the summer of 1942. Substitution therapy was instituted in September, 1943, and over a period of two months she received 12 injections of estromone, each of 10,000 international units. After this she received two injections per month, each of 10,000 international units, until January, 1944. During this course of therapy she had no subjective symptoms related to her breasts. On December 25, 1943, she accidentally discovered a lump in her right breast.

On examination, January 3, 1944, the left breast showed no significant findings. In the upper outer quadrant of the right breast was a deeply lying, freely movable mass, measuring about 4 x 2 x 2 cm. Clinically, it was thought to be a fibro-adenoma or a cyst. Local excision was undertaken on January 5, 1944.

Gross Examination.—Specimen measured 8 x 6.5 x 3.5 cm. Eccentrically located was a 3 cm. egg-shaped, delicately encapsulated fibro-adenoma which was soft and slightly edematous. Cut-surface lacked an intracanalicular appearance, and there seemed to be relatively little epithelial component. Adjacent breast tissue appeared diffusely fibrous with slight fat content. Six small cysts were present, 2-8 Mm. in diameter. Lobules appeared rather indistinct and small.

Microscopic Examination.—Sections of the mass itself showed it to be almost diffusely fibrous, with its bulk made up of partly hyalinized fibrosis and partly with more cellular connective tissue. Epithelial components were very few in number, made up of moderately dilated, inactive looking mammary ducts. The tumor scarcely represented a fibro-adenoma in the true sense of the word and might be more properly interpreted as fibro-adenomatoid mastopathy. In the surrounding breast tissue were moderate numbers of mammary lobules. None of these had a characteristic cyclic pattern. Many showed old lobular sclerosing adenosis. Others appeared as expected in a postmenopausal breast, varying stages of atrophy being present. One large lobule had frequent component parts and appeared in an early stage of apocrine transition. There were several areas of blunt duct adenosis which appeared in early phase and quite active, with considerable papillary hyperplasia of lining epithelium. In addition, there was slight papillomatosis in other ducts which did not appear to be newly formed.

COMMENT.—Perhaps the occurrence of relatively early blunt duct adenosis, with papillary hyperplasia should be mentioned. Again, the occurrence of early transitional stage in apocrine metaplasia should be noted.

Case 3.—V. S., age 30. In early December, 1939, she noted a lump in her right breast. She went at once to her family physician who gave her injections of theelin, 2,500 international units, three times per week for several weeks. This caused no local change in her breast and the dosage was increased to 10,000 international units three times per week for several more weeks. Again, there was no change noted locally, but a lump appeared in the right axilla.

When examined, February 27, 1940, in the central portion of the breast was a firm, irregular mass 5 x 5 x 3 cm., firmly attached to skin. The axilla contained a hard 2 cm. mass.

Radical mastectomy was undertaken, February 28, 1940.

Gross Examination.—In summary, there was a firm infiltrating mammary carcinoma 4 x 3 x 2.5 cm., which had no unusual characters. Surrounding breast tissue contained little fat. The lobules seemed more abundant than usual, in some areas suggesting irregular overgrowth. No gross cystic or papillary lesions.

Microscopic Examination.—Sections of the cancer showed a fully malignant, cellular infiltrating duct carcinoma, Grade III. No unusual or unexpected pathologic changes were noted which had not been seen on innumerable other occasions. Multiple axillary nodes were involved. Mammary lobules were numerous, of uniform pattern, and the only abnormalities present were those referable to pressure and distortion due to continuity with tumor. The breast tissue contained no noncancerous proliferative lesion.

COMMENT.—No significant findings in the breast tissue.

Case 4.—C. D., age 39. In 1934, a clinical diagnosis of chronic mastitis was made. No specific treatment was given until September, 1939. At this time, her left breast became firm, enlarged and tender. She was treated for several months with injections of theelin, 100,000 international units per month. Her symptoms were alleviated, and her breasts became equal in size by March, 1940. At this time, the left breast contained transilluminatable lumps. Hormone therapy was discontinued. In July, 1940, her left breast became smaller than the right and quite firm. Another course of theelin injections was given, 200,000 international units in four injections. Last injection was given on August 21, 1940.

When examined, September 12, 1940, a large, fixed mass occupied most of the left breast. Tumor was attached to skin.

Radical mastectomy was undertaken, September 17, 1940.

Gross Examination.—Most of the breast tissue was replaced by infiltrating tumor. That which remained was largely fatty. No gross lesions observed except the cancer. Multiple axillary nodes involved.

Microscopic Examination.—No cytologic features of note were found in sections of the tumor. In the remaining breast tissue there were few lobules, and these showed retrogressive atrophic changes. The only noteworthy lesion in the breast tissue was one area of blunt duct adenosis, the growth-pattern of which indicated an earlier than usual phase.

COMMENT.—Note again the character of the blunt duct adenosis.

Case 5.—H. H., age 55. In October, 1943, she noted a lump in her right breast. Two months prior to this her breasts had been examined and no mass had been palpated. The lump was painful for a time but this subsided.

Patient's menopause occurred in early 1941. Substitution therapy was begun in January, 1941. Between that date and May, 1941, she received 10,000 international units of theelin every two weeks. From June, 1941, until October, 1943, she took tablets of stilbestrol by mouth. These totalled 175, each 0.5 mg. From October, 1943, until late February, 1944, she took one of these tablets daily.

Examination, February 28, 1944, revealed moderately large, shotty breasts. In the right breast an indefinite mass, about 2 cm. in diameter, was felt adjacent to the areolar border in the 11 o'clock axis. There were no secondary skin changes and no deep fixation.

On February 29, 1944, the above mass was surgically excised.

Gross Examination.—Specimen measured 6 x 4 x 3 cm., and was tough and fibrous. On section, were a few scattered cysts, the largest not over 1 cm. in diameter. No other visible abnormality.

Microscopic Examination.—Breast tissue fibrous except for very small amount of fat. Small cysts had no residual lining. Ducts and lobules, particularly the latter, were greatly reduced in number. Some lobules showed atypical epithelial hyperplasia, and a few had the characteristic appearance of lobular carcinoma *in situ*. A few foci of apocrine epithelium were seen.

COMMENT.—Presence of a rare lesion, lobular carcinoma *in situ*, is noteworthy but justified no conclusion. Apocrine metaplasia again present. If hormone produced any alteration in this breast the effects were extremely focal, since the organ as a whole was very atrophic. Evidence of regenerating ducts and lobules was not found.

Case 6.—A. S., age 48. In 1930, an hysterectomy was performed. In October, 1941, stilbestrol therapy was commenced. She received injections of 1 mg. every other day, without interruption, for two years. This therapy was terminated October 20, 1943. The patient thought that she first noticed a lump in her left breast in October, 1942. She was not certain of the exact time of onset, but believed that the lump alternately would disappear and reappear. She had no subjective symptoms referable to her breasts. In September, 1943, she noted puckering of the skin in the region where she had noted the lump.

When examined, October 19, 1943, the skin in the upper outer quadrant was dimpled, and there was an underlying 4 cm.-tumor which was firm, irregular and partly fixed.

Radical mastectomy was performed, October 29, 1943.

Gross Examination.—The breast contained a typical infiltrating scirrhous carcinoma, 2.5 cm. in diameter. The breast tissue was more fatty than fibrous and contained many small cysts, the largest about 3 Mm. in diameter. There were no other gross lesions. The mammary lobules were inconspicuous.

Microscopic Examination.—The tumor itself was characteristic infiltrating duct carcinoma. There was extensive intramammary lymphatic invasion, and one axillary node contained metastatic tumor. The mammary lobules were very few in number. Those present showed changes secondary to the presence of the tumor and obstruction of ducts. Here and there was slight piling-up of the duct epithelium, and in one area distinct but slight papillomatosis. Multiple foci of apocrine metaplasia were present, and there were occasional scattered foci of blunt duct adenosis of slight degree and of intermediate phase.

COMMENT.—No microscopic findings of note.

Case 7.—A. G., age 38. For one year this patient had noted "tingling and drawing sensations" in her left breast. For a similar period she had been aware of a palpable lump in the lateral portion of the left breast. A somewhat more recent development was premenstrual breast tenderness, more apparent on the left than right.

When examined, February 13, 1941, there was a smooth, rounded nodule, about 3 cm. in diameter, in the lower outer quadrant of the left breast.

On April 21, 1941, Progynon B injections were commenced. Two injections were given weekly, each 6000 rat units. Six such injections were administered. Just at the conclusion of this therapy it was thought that the lump in the left breast was somewhat smaller and softer. Following the hormone therapy her menses were delayed for three weeks. The apparent alteration in character of the lump in the breast was temporary, and it regained its former character, remaining essentially unchanged. On October 9, 1941, an endometrial biopsy was done, which showed a normal premenstrual pattern. On October 16, 1941, Progynon B injections were again started and were given in 6000 rat units quantities twice weekly until ten injections had been administered. On November 17, 1941, another endometrial biopsy was taken, and this showed highly typical glandular and cystic endometrial hyperplasia.

Local excision of the lump in the left breast was undertaken, November 19, 1941.

Gross Examination.—Excised specimen measured 5 x 5 x 2 cm. It contained an encapsulated, intracanalicular fibro-adenoma, 2.5 cm. in diameter. This was freely movable in its bed. Adjacent breast tissue was almost entirely fibrous in character, and the lobules were inconspicuous. No gross lesions seen such as cysts or papillomas.

Microscopic Examination.—Sections of the fibro-adenoma were not impressive. The canalicular epithelial channels contained very orderly inactive-looking lining epithelium. They were surrounded by connective tissue which, immediately around the epithelial canals, was arranged in an edematous halo-like fashion, such as is commonly seen in gynecomastia. The cellularity of the connective tissue varied from almost hyaline to moderately cellular. In the breast tissue the lobules were rather numerous, and

they varied from small to moderate in size. Lobules not homogeneous in structure. An occasional lobule showed old sclerosing adenosis. A fair number of the terminal ducts showed distinct but not marked stratification hyperplasia of lining epithelium. Some of the mammary ducts were putting out end buds but not forming true lobules. There was one distinct area of blunt duct adenosis in a distinctly early proliferative phase. Now and then, a lobule was found with changes suggesting very early sclerosing adenosis. Some of the acinar lumina contained pinkish or grayish-pink secretory material; others contained acini with collapsed lumina. No lobules seen that were distinctly characteristic of a secretory phase of the menstrual cycle.

COMMENT.—Although there was no uniform alteration in either the fibroadenoma or adjacent breast tissue, mention is made of the appearance of the earlier phases of both blunt duct adenosis and sclerosing adenosis. This may be of some speculative interest, inasmuch, as estrogenic therapy had been begun only about six weeks before the breast material was obtained. Her previous estrogenic therapy had been completed about six months before, and was not as great in amount as the later cycle of hormone therapy.

Case 8.—M. M., age 39. In 1933, when she was 29 years old, this patient had a pelvic operation, following which her menstrual periods became irregular and scanty. For an indefinite period of years she had noted swelling of her breasts and pain just before menstruation. In October, 1941, estrogenic therapy was begun, and she received 10,000 international units of theelin weekly, and continuously, until October, 1943. In October, 1943, her family physician noted a lump in her left breast. During the period of hormone therapy the patient had no new subjective breast symptoms. No statement as to whether her premenstrual tension was increased or decreased.

When examined, October 19, 1943, there was a cystic mass, about 4 cm. in diameter, located in the upper outer quadrant of the left breast 3 cm. from the nipple. This mass was not fixed and there were no skin changes.

Mass in the left breast was surgically excised, October 29, 1943.

Gross Examination.—Specimen measured 6 x 5 x 4 cm. There was a 3-cm. smooth thin-walled cyst, contents of which had been evacuated. Surrounding breast tissue was diffusely fibrous and contained occasional cysts which varied from 1-2 Mm. in diameter. No other gross lesion was seen. The mammary lobules appeared rather small and sparse.

Microscopic Examination.—Lobules adjacent to the cyst wall showed expected secondary alterations. Lobules and ducts relatively few in number. Scattered areas of slight papillary hyperplasia in small and terminal ducts. Most definite abnormality present was blunt duct adenosis. Recent proliferative phases of this lesion as well as intermediate ones were seen. One minute focus of sclerosing adenosis was found, not in florid phase. A good many ducts had end-buds, which did not form lobules, and yet did not approach blunt duct adenosis.

Case 9.—P. N., age 20. In November, 1940, this patient began to have intermittent pain in the upper outer quadrant of the right breast. For several months this seemed to occur just before and during her menses. For four months prior to November, 1941, however, the pain was more intense, more frequent, and not related to menstruation. She had no other breast symptoms.

When examined, December 1, 1941, close to the areola in the upper outer quadrant of the right breast was a slightly irregular area of firmness, measuring about 4 x 3 x 2 cm. This area of induration was fairly well-demarcated. Several centimeters medial to this region was a discrete area, 1 cm. in diameter, which felt cystic.

The patient was examined periodically over a period of about 11 months, with essentially similar palpable findings. On November 9, 1942, she was given injections of testosterone propionate two times per week, in single 25 mg. doses. A total of 16

injections were administered, the last on January 5, 1943. The patient's last menstrual period began on December 29, 1943, and was described as normal. Toward the end of the testosterone therapy the lump in the upper outer quadrant was thought to become softer but did not disappear.

Local excision was undertaken, January 13, 1943.

Gross Examination.—The excised specimen measured 9 x 7 x 2 cm. It was more or less homogeneous in appearance, with no definitely localized lesion. The breast tissue was diffusely fibrous, and on the cut-surfaces were small numbers of rather small, glistening, slightly moist lobules. No gross cystic or papillary lesion was seen.

Microscopic Examination.—The chief feature of the microscopic examination was the difficulty in detecting a distinct abnormality. The frequency of the mammary lobules was decidedly reduced but not remarkable. The mammary ducts were correspondingly few. Nowhere in the sections was there any evidence of an unusual degree of atrophy, such as faded landmarks of lobules formerly present. If one predicted from the lobule structure the phase of the menstrual cycle at time of operation, it would be placed in an early secretory phase. Specifically present were mitoses in the acinar epithelium by no means difficult to find. Nothing of note was seen in the breast stroma.

COMMENT.—This case is briefly recorded so as to present essentially negative findings after specific hormone therapy. We have only one other case treated with testosterone in which sections of the breast are available. This case was that of a young woman who received quite large amounts of testosterone for a considerably longer period of time than the preceding case. The second case did have extremely atrophic breasts, but was a doubtful object for comparison, inasmuch, as the breast tissue was secured post-mortem in a patient with extreme cachexia from extraordinarily generalized osseous and other metastatic mammary cancer.

Case 10.—B. R., age 42. In May, 1943, the patient noticed a lump in her left breast. This was accidentally discovered, and was asymptomatic. No other breast symptoms.

The patient was known to have bilateral polycystic kidneys, with hypertension, moderate renal insufficiency, and multiple episodes of hematuria.

Her menopause occurred in 1939. Stilbestrol therapy was begun, October 29, 1942. The daily dose ranged from 0.1–1 mg. Treatment was continuous and lasted through the time of the surgical procedures to be mentioned below. Between October 29, 1942, and October 14, 1943, patient received 131.2 mg. of stilbestrol. During this time there was no uterine bleeding.

On examination, July 23, 1943, there was a 3 x 2 cm. nodule at the 6 o'clock radius of the left breast. This was irregular and hard. Right breast was described as normal. No specific statement as to the consistency of the breast tissue in either breast.

On October 15, 1943, left radical mastectomy was undertaken.

Gross Examination.—The breast contained a 2-cm. infiltrating carcinoma, of not unusual type. The breast tissue, however, was most remarkably altered. Its composition throughout was more or less similar, but not entirely uniform, since there were two large, not well-demarcated portions about 6 cm. and 4 cm., respectively, in greatest diameter. These areas bulged slightly on section, but were not encapsulated and merged rather imperceptibly with the remaining adjacent breast tissue. The exposed surfaces were extremely cellular, due to innumerable lobular units which varied from one millimeter to several millimeters in diameter. These lobular members were very closely aggregated in the two large areas noted above, but were also present elsewhere in the breast in smaller number. The predominantly epithelial nature of these small and larger lobulations was obvious, and their cut-surfaces, which were grayish-white to

CANCEROUS vs. NONCANCEROUS BREASTS

grayish-pink, were slightly elevated. Occasional fine granular streaks were seen in these areas.

Microscopic Examination.—The tumor was a cellular medullary infiltrating duct carcinoma, Grade II, composed of large cells growing in plexiform sheets. No unusual cytologic change was detected in the tumor. Sections were taken from all portions

FIG. 44

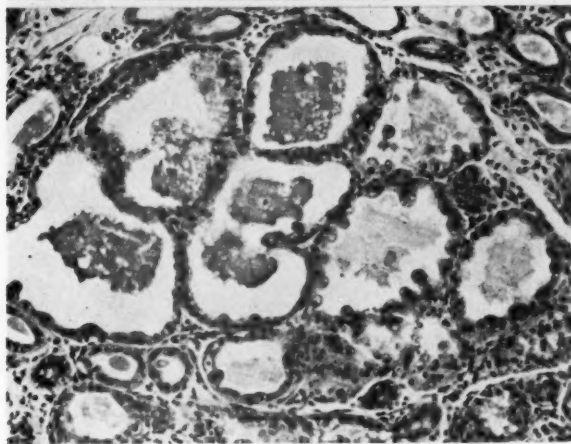
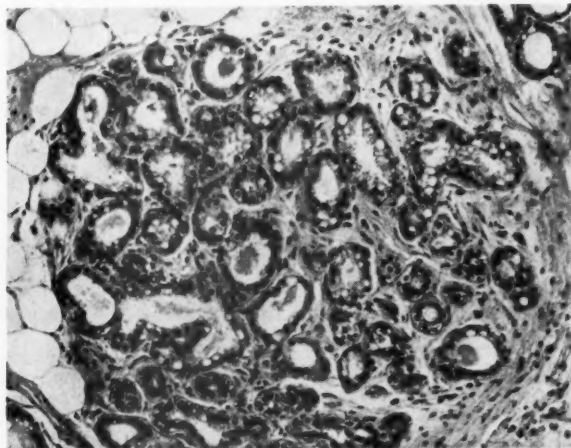


FIG. 45

FIG. 44.—Lobule with structure indistinguishable from those of lactating breast. Patient postmenopausal. Received stilbestrol therapy. (See Case 10 in text for details. Figures 44 through 47 are from the same breast.)

FIG. 45.—Similar to Figure 44, but showing exaggerated secretory structural pattern. At rare points cytoplasm becoming faint pink.

of the breast tissue, and these varied, one from the other, only in trifling degree. The composite structural pattern presented was unique and remarkable in degree, if not in kind—one not duplicated in thousands of mammary glands previously seen at this hospital. No segment of the breast was free from alteration. Here and there were scattered lobules without noteworthy configuration. These were exceptional. Almost everywhere would be met foci of sclerosing adenosis in florid phase. Merging with, and adjacent to, such lesions was much blunt duct adenosis in pronouncedly early

proliferative phase. Duct papillomatosis was a prominent feature, participating in the areas of sclerosing adenosis and blunt duct adenosis as well as in what apparently were preformed mammary ducts. The quality of the papillomatosis, for the most part, was rather orderly, but at many scattered foci, quite distant to the mammary cancer, were areas of distinctly atypical papillary overgrowth, at no point, however, sufficiently advanced to suggest a diagnosis of carcinoma.

FIG. 46

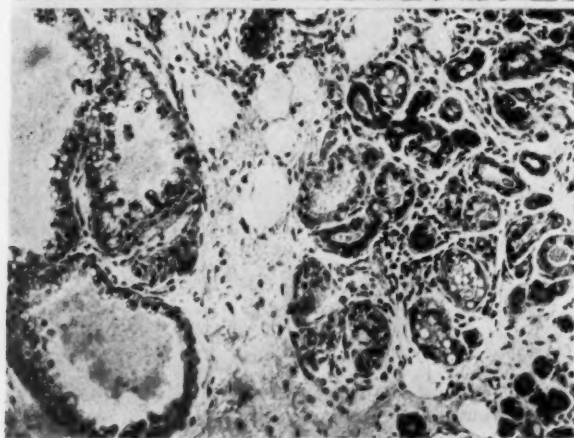
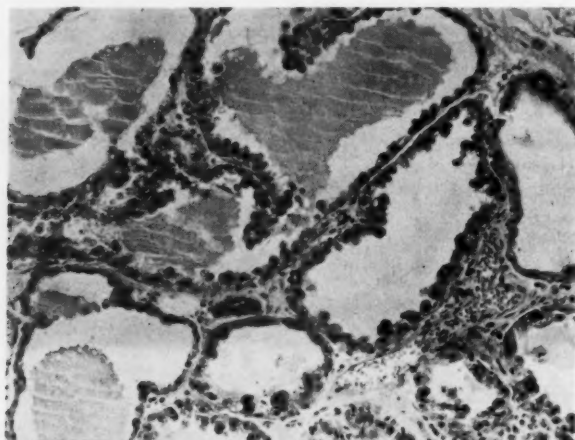


FIG. 47

FIG. 46.—Further progression in formation of apocrine epithelium. Pink-staining quality now well developed.

FIG. 47.—To show focal areas of change. At right apocrine metaplasia somewhat more advanced than in Figure 46.

Perhaps the most impressive and unexpected microscopic finding was one concerning the mammary lobules (Figs. 44 to 47). This alteration was widespread, and consisted of an exact duplication of lactating breast tissue, with large clear vacuoles in the lobular epithelium. Certainly, for the greater part, no other alternative explanation suggested itself. On close study, however, in very limited areas the vacuolization became less water-clear and developed fine pink granulation, which in turn became deeper and coarser. Finally, with coalescence of bright pink granules the cells assumed an appearance characteristic of apocrine epithelium. Such transitional areas were very

few and required careful search. Worthy of note, is the fact that in those areas duplicating lactating breast, as well as those possibly representing early phases in formation of apocrine epithelium, mitoses could occasionally be distinguished. Occasionally, there were areas of advanced apocrine metaplasia which were markedly distended and appeared cystic. In general, the proliferative phenomena throughout the breast tissue were considered in an active state, but here and there were undoubted areas of focal regression.

Relatively little connective tissue intervened between the epithelial portions of the breast, and in this was a moderate amount of fat. The fibrous connective tissue for the most part was fairly loose, but not unusually cellular or particularly vascular. The intralobular connective tissue contained, variously, very few to considerable numbers of round cells, chiefly lymphocytes, but also fairly plentiful plasma cells.

COMMENT.—The extraordinary structural features seen in the breast of a patient who had received 131.2 mg. of stilbestrol for a period of one year prior to radical mastectomy, naturally, raises the question of causal relationship between the hormone therapy and the lesions produced, including both the mammary cancer and the alterations in the breast tissue. This patient first noted a lump in her left breast in May, 1943, which was approximately six months after the start of the stilbestrol treatment. It had necessarily been present for some time prior to discovery, and considerable mass is required to make such a discovery possible. The time-factor hardly favors a view that the hormone caused the development of cancer. If one assumes that the hormone provoked particularly aggressive growth-capability in the tumor, this appears unlikely, inasmuch, as the axillary lymph nodes did not contain metastatic deposits and there was no outstanding intramammary lymphatic penetration or cytologic quality of excessively active growth.

It is tempting in this case to relate the extreme alterations in the breast tissue to hormone therapy. Satisfactory support for this is not easy, since observations on breast tissue changes, following administration of estrogenic substances, are so limited. On the basis of observations presented here, in cases receiving estrogenic therapy, insufficient similarity of structure had been induced to make these breasts recognizable as a group that had been so treated. They did not, however, receive equivalent amounts of hormone, and temporal factors varied from case to case. But even if dosage and time factors had been equal, homogeneity of structure can scarcely be demanded, since this necessitates that every breast respond in the same way. We doubt if more than a trend will ever be shown. The not unreasonable theory is suggested that certain individuals possess mammary epithelium which is more than ordinarily responsive to estrogenic stimulation. The highly diffuse and exaggerated alterations seen in the case under discussion correspond to this mode of thought. The case offers something in contrast with Case 7, in which the endometrium seemed to be more labile to estrogenic stimulation than the breast, whereas, in the present case the breast tissue appeared to be the more labile. Before adopting this theory of selective susceptibility, however, it is advisable to await the appearance of similar cases encountered under similar conditions. The few cases presented here need to be multiplied

several times before sufficient material is available to point out trends in lesion types.

In the present case there is one factor of possible consequence in the action of the stilbestrol that the patient received, namely, the presence of renal insufficiency due to polycystic kidneys. Perhaps with a deficient renal mechanism the excretion of this substance was retarded, and there was a resultant enhancement of action. The total amount of stilbestrol received over a period of one year in this case was not excessive.

In connection with this case we refer briefly to a recent publication of Engle, Krakower and Haagensen,³⁹ describing the results of intensive and sustained estrogenic administration to mature female monkeys. In their experiments the morphologic effects on the uterus, including glandular and cystic hyperplasia, far overshadowed any of the findings described in the breast. Another bit of evidence of threshold influence in mammary response is cited in the commonly unilateral nature of gynecomastia. Allen⁴⁰ found in male mice treated with estrogens that some of the mammary rudiments did not respond while others in the same animal did. The varied responses in mammary glands of different species are impressive. Since the breast tissue from the left radical mastectomy in Case 10 contained many areas structurally like late gestational or lactating breast, a recent experiment of Reece⁴¹ is of interest. By injecting diethylstilbestrol propionate he was able to induce full milk flow in sterile heifers.

Additional Note on Case 10: This patient's left radical mastectomy was undertaken on October 15, 1943. The stilbestrol therapy had been discontinued, October 7, 1943. On follow-up examination January 27, 1944, a one-centimeter mass was felt in the right breast. Aspiration biopsy was done and was reported as carcinoma. On account of the patient's generally poor physical condition, a modified mastectomy was performed, February 24, 1944.

Dissection of the operative specimen revealed a characteristic infiltrating carcinoma, 2.5 cm. in diameter. This had every gross feature of a new primary lesion. In the fibrous breast tissue there were multiple lobulated areas resembling sclerosing adenosis. No cysts or duct papillomata were seen.

Sections from the tumor disclosed a cellular growth-pattern, with large cells that had relatively abundant cytoplasm. At many areas in the tumor the cytoplasm was pale pink and sometimes finely granular, with more than casual resemblance to apocrine epithelium. The structure of this breast tissue showed many traits in common with that seen in sections of the left breast. Every lesion seen in the left breast was also observed in the right breast. The abnormalities were very widespread. Quantitative differences were apparent. One chief difference was considerable reduction in amount of tissue resembling lactating breast. Apocrine metaplasia was more in evidence. All transitional stages were represented. Papillomatosis in small ducts was more marked and had more atypical features. Sclerosing adenosis was more extensive and continued to be in florid phase. Actively proliferating blunt duct adenosis was present at multiple foci, and there were occasional intermediate phases of this change. Of interest was the fact that in the second breast mitotic activity, though not prominent, was more frequent in the abnormal lobular proliferations than was found in the preceding breast. In summary, comparison of these two breasts, sections from the second mastectomy revealed diminution of the lactation-like areas with moderate other proliferative phenomena.

COMMENT.—Even though a second primary tumor developed in this case, it is still not easy to attribute its causation to hormone therapy. The tumor, 2.5 cm. in diameter, was not a small one. It would appear safer to assume clinical oversight in the recognition of the tumor rather than to believe that no tumor was present when this patient was first examined in July, 1943, and at later visits. Just prior to the second mastectomy the tumor was described clinically as being one centimeter in diameter. The mere fact that it was 2.5 times this large forces one to suspect that the tumor was present long before detected. In view of preceding discussion, the resemblance of the cancer cells in many areas to apocrine epithelium is mentioned. Pink-staining quality was lacking in the cytoplasm of the cells of the initial tumor, but with this exception the cells in the two cases were comparable.

Whether, or not, the right breast tissue was structurally more like that of the left breast three months prior to the right mastectomy is, of course, impossible to say. To be sure, fundamentally, the same group of lesions was present in each breast with certain differences in degree as outlined above. Present observations are not sufficient to be sure that withdrawal of the hormone was followed by partial involution of the secretory looking areas. Nor is it possible to state that the more abundant apocrine epithelium found in the second breast represented a metaplastic by-product in such an involutional process. Other lesions including sclerosing adenosis, blunt duct adenosis and papillomatosis exhibited no regressive tendency in sections of the second mastectomy. No great importance attaches to this, however, for there is good reason to believe that they may maintain a florid or active phase for long periods of time.

At most, this rather unique case furnishes guidance for future observations. A single case is not crucial, but a modest number of even less striking examples would reinforce a positive point of view, not only for the causation of certain noncancerous lesions by administration of estrogenic substances, but the modification of certain lesions following withdrawal.

In summary, the breast tissue from nine cases treated with estrogenic substances has been examined. The structural characters of these breasts were not sufficiently specific to constitute a distinct pathologic complex. Similarities as well as dissimilarities were present. Changes of kind and degree were found. One case was regarded as highly exceptional. Some suggestion of trends may be proposed such as the finding in several cases of earlier phases of blunt duct adenosis, sclerosing adenosis and apocrine metaplasia. The occurrence in one case of lobular carcinoma *in situ* calls for continued attention to this lesion. Over a long period of time enough material may accumulate to support or reject whatever point of view one now chooses. The pleomorphic character of various responses of the mammary gland may in the future be largely explained on a basis of individual susceptibility and reactivity.

CONCLUSIONS

1. Atrophy of the breast as judged by the number of lobules present depends upon the factor of age, and does not differ in cancerous *versus* noncancerous breasts.

2. Macroscopic cysts are much commoner in noncancerous breasts, particularly in women between 40 and 50 years of age. During this period they are least common in cancer-containing breasts.

3. No distinct difference in the frequency and extent of duct papillomatosis is found in cancerous and noncancerous breasts. Macroscopic papillomas are somewhat more common in noncancerous breasts. Cancer-containing breasts are about five times as apt to show papillomatosis which is cytologically atypical.

4. Every transition from atypical papillomatosis to duct cancer can be traced microscopically, such phases being demonstrable on occasion in a single breast.

5. Blunt duct adenosis appears to be a common precursor to cyst formation. In cancerous breasts between the fourth and fifth decades blunt duct adenosis is the most common, and cysts are comparatively few, indicating, in this class of breasts, that blunt duct adenosis tends to retain its proliferative capacity.

6. The origin of mammary cancer can be traced histologically to blunt duct adenosis in only a very few cases.

7. Apocrine epithelium is common in both cancerous and noncancerous breasts, and of not pronouncedly different character. Rare cases of mammary cancer can be traced to this source.

8. Sclerosing adenosis in cancerous as opposed to noncancerous breasts shows no outstanding differences. The early or "florid" phase is more common in younger women, but can be observed as late as the sixth decade.

9. The triad of lesions including stasis of duct content, duct dilatation and periductal mastitis exhibits similar traits in both cancer and noncancer-containing breasts. No evidence was obtained that they furnish a starting point for development of mammary carcinoma.

10. Two forms of periductal mastitis can be distinguished—primary and secondary. The latter is more common.

11. Structural abnormalities of the mammary lobules are described. These can be separated into two groups referred to as primary and secondary lobular alteration.

12. Intralobular hyperplasia of pathologic type can be shown in some cases to merge gradually with lobular mammary carcinoma *in situ*.

13. Evidence is presented that the true component parts of "chronic cystic mastitis" should include (1) cysts; (2) duct papillomatosis; (3) blunt duct adenosis; (4) apocrine epithelium; and (5) sclerosing adenosis. Perhaps a sixth lesion, primary lobular alteration, may be included. Fibroadenoma is excluded.

14. Estimations of the frequency of so-called chronic cystic mastitis

depend upon what and how many lesions are deemed essential in making that diagnosis.

15. Statistical and morphologic studies indicate that chronic cystic mastitis does play a rôle in the development of human breast cancer. How large this is we cannot state. Our studies suggest that its part consists largely in those papillary hyperplasias which in some individuals, for reasons unknown, become cytologically atypical. In other words, some people cannot handle the hyperplasias which to others seem controllable and innocuous.

16. The pathologic findings in breasts from nine women treated with estrogenic substances are recorded. In one case remarkable structural features were present and these were fully discussed.

17. The failure of the breast tissue to respond uniformly to administration of hormone may depend upon individual differences in susceptibility. Thresholds of reactivity may vary through a broad range. Judged by the few cases available for study to date, wherein, with one notable exception treatment by estrogens has produced no noteworthy specific alteration in breast structure, one can at least say that no progressive series of changes beginning with a normal breast and ending with mammary cancer has been encountered. In the exceptional case, whereas, hormone alterations were, indeed, profound, there were reasons to doubt their significance in the production of the cancer.

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STUDIES IN SURGICAL CONVALESCENCE*

II. A PRELIMINARY STUDY OF THE NITROGEN LOSS IN EXUDATES IN SURGICAL CONDITIONS

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THIS REPORT, an outgrowth of studies on the nitrogen balance in surgical conditions, represents an attempt, quantitatively, to determine how much body proteins in the form of nitrogen is lost in the exudates of exudative surgical conditions. The values are random ones, and are reported out of their case-setting because, in many cases, they are of such magnitude as to be of importance to the practicing surgeon. It is apparent that unless large losses are replaced by special measures of alimentation, recovery from these conditions will be retarded or even jeopardized.

Thirteen cases, typifying four surgical conditions are included in this report. They are: (1) Surface burns; (2) avulsion; (3) seepage from areas of extensive surgical dissection, both infected and uninfected; and (4) local infective conditions, such as lung and liver abscess.

METHODS

A number of difficulties attend the collection of material from an actively exuding surface. Surgical gauze dressings do not lend themselves to this purpose quantitatively because their retentive capacity is small, resulting in an overflow which seeps through into the bedding. Moreover, gauze is difficult to dissolve, sometimes taking as long as a month to six weeks to attain complete solution in sulfuric acid. Accordingly, in only three cases was gauze used. In ten, the following method of exudate collection was followed: Slabs of fine cellulose sponge (Du Pont) 0.25 x 10 x 5 inches were rendered nitrogen-free, by soaking them first in tap water for at least 12 hours and then rinsing them in distilled water three times. After drying at room temperature for about 24 hours, they were wrapped in cloth and sterilized in the autoclave. Before being applied to the exuding surface, they were moistened with physiologic saline solution. After application, the slab was covered with cellophane of medium thickness, extending beyond the edges of the sponge for about five inches, *i.e.*, far enough to prevent seepage

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of the exudate beyond the edges of the cover. This sponge was usually left in contact with the exuding surface for from 24 to 48 hours. At the end of this period, it was transferred to dilute sulfuric acid for digestion. Both the cellophane covering and the skin beyond the exuding surface were wiped with pieces of moistened cellulose sponge, which were, likewise, placed in the sulfuric acid together with the sponge-dressings. It took about a week to bring the sponge into complete solution, after which an aliquot part was taken for nitrogen determination according to the method of Levy and Palmer.¹

RESULTS

Table I summarizes all the 13 cases, with columns showing the nitrogen loss in terms of proteins and cubic centimeters of plasma.

Table II is a rearrangement of the cases of burns listed in Table I, in the order of the percentages of body surface involved. F. W. was listed twice in the table and J. Mc. three times, because their exudates were collected, one, twice, and the other, three times at different age-periods of the burns. There seems to be a rough parallelism between the percentage of body surface involved and the magnitude of nitrogen loss. However, other factors enter here to modify the picture, namely, how much of the wound is involved in second and how much in third degree burns; and how much tissue has been converted into an eschar, which would seal off exudation until it is sloughed off. Thus, while J. Mc., whose burns were mostly second degree, showed a progressive decline in the magnitude of nitrogen loss as the burned area aged, F. W. showed a small loss of 1.58 Gm. on the eighth day, when the burned area covered only 10 per cent, while on the fortieth day, when the burned area covered only 8 per cent, it was 4.07 Gm. J. Mc. had a burn which was not covered by an eschar, while F. W.'s burn was. The figures for M. W. and A. F. were, respectively, 6.45 Gm. and 9.17 Gm., representing 40 per cent of exuding surface on the ninety-fourth day and 50 per cent on the fourth day, respectively, were minimum figures since gauze was used for collection. These figures merely signified that at least this amount of nitrogen loss was sustained.

J. Mc.'s figures suggested the possibility of an attempt on the part of the body to reduce nitrogen loss as the wound aged. The values of Hirschfeld, and his coworkers² seem to confirm this tendency. However, as mentioned before, this tendency would be modified by the presence of an eschar, and perhaps by other factors to be mentioned later.

Polar planimetry was performed on four of these cases in order to determine the nitrogen loss per unit area. The loss ranged from 1.25 mg. on the sixth post-burn day, in J. S., to 2.95 mg. for the tenth day in F. W., and 3.28 mg. for the twelfth day in J. W.

S. S. is an example of the second type. He suffered an extensive avulsion of the back, buttocks and perineum. The skin surface was infected and the exudate was of a seropurulent character. His loss of nitrogen was 6.37 Gm.

STUDIES IN SURGICAL CONVALESCENCE

TABLE I
NITROGEN LOSS IN DIFFERENT EXUDATIVE SURGICAL CONDITIONS

Name and Sex	Diagnosis	Date of Injury or Operation	Date of Collection	Surface Involved Sq. Cm.	Total N. Exuded in 24 hrs.		Equiv. in 24 hours. Proteins Gm.	Equiv. in Plasma CC*	Collecting Material
					Gm.	Mg.			
M. W. (M)	Burns, 2nd. and 3rd°.	2/ 8/43	5/11/43	40	6.45 +		40.31 +	672 +	Surg.† gauze
A. F. (M)	Burns, 2nd. and 3rd°.	6/ 3/43	6/ 7/43	50	9.07 +		58.80 +	345 +	
J. Mc. (F)	Burns, 2nd. and 3rd°.	7/ 1/43	7/ 7/43	30	5.15		32.19	537	
			7/18/43	21	3.56		22.25	373	
			7/22/43	15	2.98		18.62	310	
A. B. (F)	Burns, 2nd. and 3rd°.	11/10/43	11/12/43	20	1.5		9.4	150	
J. W. (F)	Burns, 2nd. and 3rd°.	12/21/43	1/13/44	15	7.65	3.28	47.79	798	
F. W. (F)	Burns, 2nd. and 3rd°.	1/15/44	1/23/44	10	1.38	0.9	9.64	164	
			2/25/44	8	4.07	2.05	25.44	424	
J. S. (F)	Burns, 2nd. and 3rd°.	2/ 4/44	2/ 8/44	15	1.79	0.64	11.39	189	
S. S. (F)	Avulsion of perineum and back	7/ 7/43	10/23/43	15	6.37	2.1	39.81	664	
R. W. (F)	Radical mastectomy	10/25/43	10/26/44		4.20		26.65	445	
			10/30/44		1.2		7.50	125	
A. G. (F)	Abdomino-perineal resection (cancer of rectum)	8/13/43	8/14/43		6.22		38.87	644	
O. Mc. (F)	Abdomino-perineal resection (cancer of rectum—infected)	8/ 9/43	8/16/43		2.07		12.97	216	
F. C. (M)	Lung abscess—Pyothorax	4/17/43	8/21/43		6.97		42.48	707	
H. L. (M)	Liver abscess (5 cm. diam.)	12/26/43	4/24/43		3.47		21.68	723	
			12/28/43		9.57 +		59.8 +	393 +	Surg. gauze
					1.38		12.63	210	Cell.‡ sponge

* The assumption is made that the protein content of plasma is 6 gm. %.

† Surg. =Surgical.

‡ Cell. =Cellulose.

TABLE II
CASES OF BURNS REARRANGED ACCORDING TO PERCENTAGE OF BODY SURFACE INVOLVED

Name	Body Surface Burned	Age of Burns (Days)	Nitrogen Loss (Gm.)
1. F. W.....	8%	40	4.07
2. F. W.....	10%	8	1.58
3. J. Mc.....	15%	21	2.98
4. J. W.....	15%	23	7.65
5. J. S.....	15%	4	1.79
6. A. B.....	20%	2	1.5
7. J. Mc.....	21%	15	3.56
8. J. Mc.....	30%	6	5.15
9. M. W.....	40%	94	6.45
10. A. F.....	50%	4	9.07

on the 108th day after injury, representing 2.1 mg. of nitrogen loss per sq. cm. of raw surface, equivalent to 39.2 Gm. of protein, or 654 cc. of plasma. This patient was kept in excellent nutritional condition and gained weight in spite of the nitrogen loss, which must have been of considerably larger magnitude during the earlier course of his convalescence.

The third type consisted of two conditions in which, as a result of extensive dissection, areas of raw exuding surface had been exposed. In R. W., a radical mastectomy was performed, the exudation of nitrogen in the blood-tinged fluid was 4.26 Gm. during the first 24 hours, dwindling down to 1.2 Gm. after four days, a decrease of approximately one-third of the original value. A. G. was a case of abdomino-perineal resection for carcinoma of the rectum. The exudate in the first 24 hours contained 6.22 Gm. of nitrogen, dwindling down to 2.07 Gm. on the third day, which was less than half of its original value. The values in these two cases suggest a tendency in clean operative wounds to rapidly seal off exuding points.

On the other hand, infected operative surfaces cannot be expected to reduce exudation as promptly. This seems to be true of O. Mc., who was also a case of abdomino-perineal resection, frankly infected, the infected area having been drained secondarily, nine days postoperatively. Here the nitrogen exudation was 6.97 Gm. the day after drainage was instituted, decreasing to 3.47 Gm. in five days. H. L. was a case of liver abscess, 48 hours after drainage was instituted, and F. C. a case of lung abscess with secondary pyothorax. Since gauze was used for the collection in this last case, this loss of 9.57 Gm. of nitrogen is also a minimal figure.

DISCUSSION.—The protein loss in the exudates in burns and other surgical conditions has not attracted serious clinical attention until recently. Lucido,³ in his metabolic study of one case of burn, to our knowledge the first one to be attempted, recognized the incompleteness of the study when the nitrogen lost in the exudate could not be determined. The report of Taylor's group⁴ on the difficulty of maintaining nutrition in the cases of burns involving over 10 per cent of body surface suggests the importance of undertaking such a study. Hirschfeld and his group have made a promising beginning, introducing a practical method of collection. Unfortunately, only one of their cases had extensive burns (35 per cent), the others involving only from 3 to 5 per cent of body surface. The report of Co Tui's group⁵ on the

comparative ease with which cases of extensive burns may be kept in good nutrition and at a fairly normal plasma level by hyperalimentation with amino-acid mixtures (Amigen) suggests a way of adequately meeting the need for the large amount of protein replacement sometimes impossible to effect by feeding natural food. These last authors also used polar planimetry in order to determine quantitatively the loss per unit area.

If the variability of the protein content reported in the literature on blister fluid is an indication, the amount of protein lost in the exudate would be expected to vary within a fairly wide range. Thus, Mörner,⁶ in 1895, reported the protein content of the blister fluid in one case of burns as 5 Gm. per cent. Wells,⁷ in 1925, reported the range as between 4 to 6.5 Gm. per cent; while McIver⁸ gave a finding of 3.7 Gm. per cent. Both Wells and Pack⁹ commented on this variability, the latter stating: "Blister fluid may be an exudate or a transudate, depending upon the degree of irritation. With more intense irritation, the capillary permeability is so altered that the fluid resembles plasma, rather than serum. A clear serum within the blebs becomes cloudy in 24 hours." This clouding, in all probability, is caused by the leukocytic infiltration. In view of the relation of the protein content to the intensity of injury, Cornbleet's¹⁰ attempt to relate the content of blister fluids to the Donnan equilibrium becomes of more academic than practical interest, at least in burns.

It is interesting in this connection that Glenn, Muss, and Drinker¹¹ found that the lymph from the burned extremity of calves is increased not only in the speed of flow, but also in protein contents, by 35 to 75 per cent.

The protein content of the blister fluid, however, is not representative of the protein content of the exudate from burned areas, particularly in late cases. Where extensive tissue destruction has taken place, the separation of the eschar opens up not only the lymphatic channels, but exposes capillaries with different degrees of injury, from which may exude, according to the severity of the injury, any blood element ranging from albumin to whole blood. Where an infection coexists, there is also protein loss from local autolysis and tissue destruction.

The losses per unit area as revealed by polarimetry in the cases of burns are significant. The highest figure was shown by J. W. on the 12th day, when 3.28 mg. of nitrogen was lost per sq. cm. of surface. At this rate, an average person with 50 per cent of his 1.8 sq. meter of surface involved in burns, could lose 185 Gm. of protein in 24 hours, an amount which would deplete the blood almost entirely of its osmotic component.

In view of the constant protein drain, sometimes of enormous magnitude, the difficulty of keeping patients with considerable burnt areas in good protein nutrition, as reported by Taylor, and his group,⁴ is understandable. These authors had recourse to heroic forced feedings, taking considerable trouble and valuable material (plasma and plasma albumin) to keep the cases of severe burns from too severe an emaciation.

When it is realized how much depends upon an effective healing process

in convalescence in burns, and when it is known how the healing process depends upon adequate protein nutrition, the vicious circle introduced by a constant protein drain, with consequent delayed healing, and, therefore, with further protein drain, the importance of the subject can be visualized. This is the more clearly seen if a skin grafting is attempted which further opens up new areas of protein loss, leading to the danger, on the one hand, of inducing shock in a person already hypoproteinemic, and on the other hand, of jeopardizing the taking of such grafts on a malnourished base. What has been said of the relationship between wound healing in burns and the state of nutrition can also be said of the other conditions herein repeated.

In cases of extensive surgical dissection (R. W. and A. G.) it is interesting to note that the losses can run up to almost 5.9 Gm. of protein in 24 hours, equivalent to 644 cc. of plasma. This, of course, includes blood. When it is remembered that with this loss outside of the body, there must doubtless be a loss of protein into the traumatized tissues in the area of the dissection, the danger of surgical shock from this cause, alone, is at once apparent. It is, however, reassuring to know that in both of these cases of widespread dissection, the protein loss fell off rather rapidly during the subsequent days.

The case of lung abscess and pyothorax (F. C.) requires some comment. The nitrogen loss of at least 9.57 Gm. per day, represents almost all the nitrogen intake in a basic diet and half of the intake in a higher protein diet. In view of this magnitude of nitrogen loss, it is clear why this type of chest cases are so often emaciated and why the mortality rate should be so high.

It may be pertinent in this discussion to bring up a point which is still undeveloped and needs further elaboration. It is the necessity of differentiating between protein loss, which involves protein drain from the entire system, and protein loss, which does not. In the former category may be placed loss of all blood and lymph elements, and to a less degree of urgency, loss of tissues which must be regenerated. In the second category may be placed protein loss involved in losses of parts of the body, such as of the breast in the case of R. W., and of extremities in amputations. Here the actual protein loss involved in the loss of the parts is larger, but since the parts are not to be replaced, it involves comparatively no protein drain to the system. It does not jeopardize health to the extent that a much smaller loss in the first category involves. In fact, it is quite conceivable that the loss of nitrogen from the exuding surface left by the excision of the organ, if it continues could be more detrimental to the body than the large amount lost in the original part. How much of one or the other factor is present in the protein loss in pus and in exudate from infected surfaces is difficult to determine.

It might also be of interest to bring up the question of the adequacy of the civilian hospital diets to support nutrition in cases of large protein drain. The "basic diet" or "standard diet" recommended by the National Research Council, on the basis of Sherman's¹² survey, in 1920, contains 70 Gm. per kilo-

gram of body weight, or 11.2 Gm. of nitrogen. Recommended as a maintenance diet, it has been adopted generally as a basic hospital diet. Since this diet is supposed to provide a margin of safety of from 50 to 100 per cent, it may be assumed that the minimum nitrogen requirement has been placed by Sherman as from 5-6 to 7.5 Gm. per person, giving a margin of safety of 3.7 to 5.6 Gm. The nitrogen loss in most of the 13 cases in Table I is larger than this margin at some stage of the convalescence; and for this reason, this diet is inadequate for this type of case. This inadequacy becomes evident when one remembers that this gram-for-gram matching has left out of consideration that the loss of urinary nitrogen is markedly increased in a large number of disease conditions of this type, and that it takes more than one gram of ingested nitrogen to cover one gram of nitrogen lost from the body.

The "high protein" diet consists of from 120 to 130 Gm. of protein (19 to 21 Gm. of nitrogen), and should be adequate to replace moderate amounts of protein drain, provided pain, anorexia and other upsets do not reduce this intake. In patients with extra metabolic protein drains of above 5 Gm. per day, even this higher protein diet may not be adequate.

Two practical implications of the foregoing discussion may be set forth: The first, applicable to the civilian hospital, is that the protein content of the "basic diet" should be increased in order to provide for a larger margin for the replacement of increased nitrogen loss in disease—offhand, a 50 per cent increase would not be too much. The second, applicable to the practicing physician, is that he develop an awareness for not only the vitamin, but, also, for the caloric and nitrogen needs of the patient, particularly in conditions which involve large losses of proteinous body fluids, and that he familiarize himself with the methods of special alimentation now available, namely, the use of amino-acid mixtures orally or parenterally. If natural alimentation fails, these measures may be of critical value. Plasma transfusions, generally speaking, should now be reserved for more emergent uses, such as correction of an acute hypovolemia.

Mention has been made of the advantages of introducing precise surface measurements into this study. This greater degree of precision may throw light on the following points:

1. The relation between the rapidity of healing or contraction of the lesion, and the general protein nutrition of the patient.
2. The differences in the amount of protein loss associated with the different tissue planes involved.
3. Evolution of the amount of exudation as the lesion ages.
4. Determination of whether different types of infectants excite different rates of protein loss.
5. The effect of local therapeutic measures on the amount of exudation.

However, it is to be remembered that the determination of the area of

skin involved in a burn is not necessarily the same as the absolute area available for exudation, any more than is the measurable area of the intestinal mucosal surface the same as that offered by the villi for absorption. In the case of the burned area, the crypts and folds and other irregularities in the denuded surface may be roughly compared with the intestinal villi in multiplying the effective absorbing surface.

Finally, it is to be mentioned that the above study is a random one. A more complete study, involving a continuous record, not only of the nitrogen loss in the exudates, but also in the urine and feces, is indicated. The method devised by Hirschfeld, and his group,² and modified to throw light on the above points, may well serve as a pattern.

SUMMARY

1. The exudate of 13 surgical cases, representing four surgical conditions, were analyzed for nitrogen contents.
2. The nitrogen losses were, in some cases, of sufficient magnitude to jeopardize recovery.
3. The significance of such losses, and the indications for a more exhaustive study were discussed.

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THE EFFECTS OF TEMPERATURE ON THE DIGESTION OF COLLAGEN SUTURES AND SURGICAL GUT (CATGUT) BY ENZYMES AND BY THE SUBCUTANEOUS TISSUES OF THE FROG*

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NATIVE COLLAGEN FIBERS from the skin or tendons are extremely resistant to enzymes, but when mechanically comminuted to very small particles or heated they become fairly readily digested by enzymes (Sizer¹). Relatively resistant acid-swollen beef tendons can be macerated into dilute suspensions (though the collagen may not pass through filter paper) and subsequently reprecipitated to reform fibers of similar ultrastructure to the original (Schmitt, *et al.*,² and Bear^{3,4}). Such treatment renders them relatively digestible by many different animal and plant enzymes. Similarly, the fibers are digested and absorbed after implantation in the animal body, and the available evidence suggests that this action is brought about by enzymes liberated from white blood cells.

The effects of temperature upon the digestion of collagen have been studied in a qualitative manner mostly by leather chemists interested in the action of enzymes during the bating of hides (cf. Wilson⁵). Using crude collagen preparations in the form of hide powder, Thomas and Seymour-Jones⁶ reported that appreciable solution by trypsin occurred at 40° C. but was very slight at 23° C. Similarly, Merrill⁷ studied the action of trypsin on hide powder by measuring the increase in soluble nitrogen during digestion, and his data indicate a threefold increase in rate from 15° C. to 25° C., a nineteenfold increase from 25° C. to 35° C., and a sixfold increase from 35° C. to 45° C. On theoretical grounds, however, the digestion of collagen by trypsin might be expected to increase exponentially with temperature in accordance with the Arrhenius' equation* (for a review cf. Sizer⁸), since this is the case for the action of trypsin on several different proteins (Butler,⁹ and Sizer

$$* \mu = \frac{4.6 (\log k_2 - \log k_1)}{1/T_1 - 1/T_2}$$

and Josephson¹⁰). The present work was undertaken with the purpose of studying quantitatively the action of proteases on collagen as a function of temperature and comparing these results with those on the digestion of collagen implanted in the subcutaneous tissues of the frog.

* This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts Institute of Technology.

METHODS

The collagen used in these studies was either in the form of collagen sutures or plain commercial surgical gut sutures (size No. 0000) prepared from sheep gut. The digestion of collagen or catgut sutures by enzymes has been studied by the method of Jenkins and Hrdina,¹¹ as modified by Lion and Sizer.¹² It consists in attaching a two-gram lead weight to the suture and immersing the suture in a test tube of enzyme solution incubated in a water bath with a temperature control of $\pm 0.05^\circ \text{C}$. The free end of the fiber is connected to a telephone message counter driven by an electric clock. When the suture is digested the lead sinker falls, a circuit is broken, and the digestion time in minutes may be read directly from the counter. A few drops of toluene are added to the enzyme solution to prevent bacterial growth. The pepsin solutions at p_{H} 2.0 contained 0.1 per cent concentrated HCl, while the other enzyme solutions were not buffered and the p_{H} was about 7.

For the animal experiments medium-sized winter frogs were used. The sutures were implanted subcutaneously, after ether anesthesia, by lifting up a fold of the abdominal skin and passing through it a suture threaded to a surgeon's straight needle. One of the free ends of the suture is slipped beneath the skin, while the other is tied to the skin with surgical silk at the point of insertion. Three sutures were implanted in each frog and, at successive intervals, samples were withdrawn. The extent of digestion was measured by determining the breaking strength of the washed and dried fiber as compared with the original sample before implantation. During the course of the experiment the frog was kept in a cage which was immersed in a constant temperature water bath. Although the frog could move about in the cage, it was impossible for it to lift its abdomen, containing the sutures, out of the water.

A. DIGESTION OF COLLAGEN AND CATGUT SUTURES BY TRYPSIN AND PEPSIN

Using the weighted fiber-breaking time technic, the digestion of sutures has been studied over the temperature range from 1° to 60°C . When log rate is plotted against the reciprocal of the absolute temperature (Fig. 1) the points fit along a straight line up to 45°C ., above which the points fall from the line due to temperature inactivation (denaturation) of the enzyme. The slope of the line corresponds to an activation energy of 31,000 cal. per Gm. mole.* for both pepsin and trypsin. It is very surprising that the same activation energy characterizes the action of both pepsin and trypsin on collagen, since the activation energy usually is different for each enzyme (Sizer⁸). In accordance with results on other enzymes the activation energy is independent of the purity of the enzyme, since the same value is obtained

* "Mole" is defined as "the weight in grams equal to the molecular weight." (*Chemical Handbook*)

SUTURE DIGESTION

(Fig. 1) for 10 per cent crude trypsin (Cenco) partially purified trypsin (Cenco, purified by using only the aqueous filtrate) and also in preliminary experiments with crystalline trypsin (Lehn and Fink). Similarly, the same values characterize crude 10 per cent (Cenco) and crystalline 0.1 per cent (Lehn and Fink) pepsin.[†] The activation energy is also independent of the

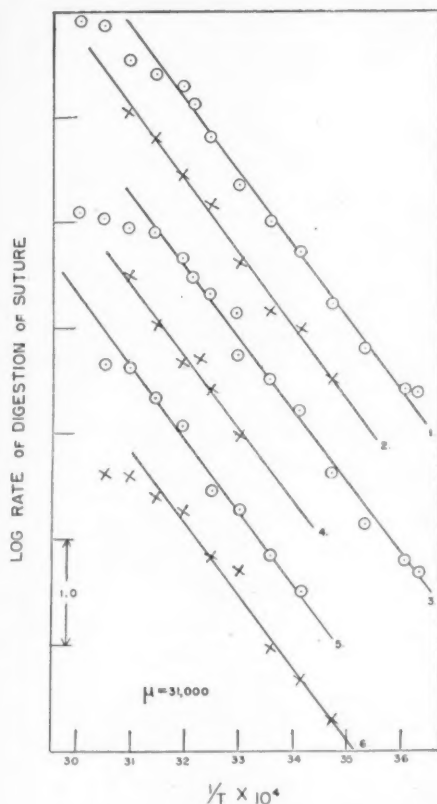


FIG. 1.—Log rate of digestion of collagen and catgut sutures in enzyme solutions is plotted against $1/T$. The same activation energy of 31,000 cal. per Gm. mole. is obtained in all cases.

1. Collagen sutures in 10% crude trypsin
2. Collagen sutures in filtered 10% trypsin
3. Collagen sutures in 10% crude pepsin
4. Collagen sutures in 1% crystalline pepsin
5. Catgut sutures in 10% crude trypsin
6. Catgut sutures in 10% crude pepsin

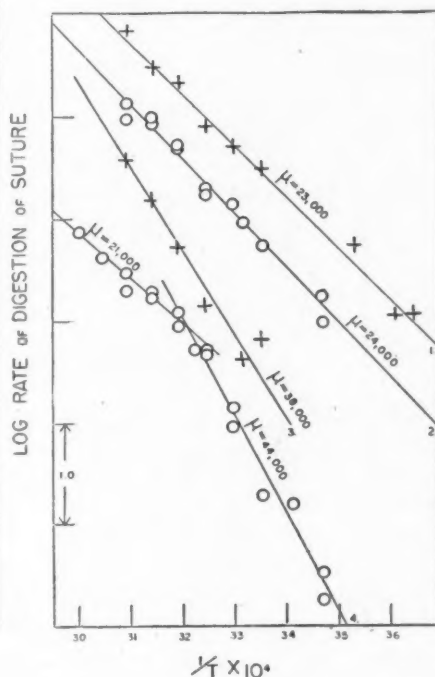


FIG. 2.—Log rate of digestion of collagen sutures in enzyme solutions is plotted against $1/T$.

1. 0.1% crystalline chymotrypsin, $\mu = 23,000$ cal.
2. 1% orthozyme, $\mu = 24,000$ cal.
3. 1% keralin, $\mu = 38,000$ cal.
4. 1% papain, $\mu = 21,000$ above and 44,000 cal. below 38°C .

source and purity of the collagen, for the same activation energy is obtained with collagen fibers (either mono- or multifilament) from relatively pure collagen of beef tendon and plain catgut sutures from relatively crude collagen of sheep intestine.

[†] In occasional experiments with both crystalline trypsin and pepsin an activation energy of 22,000 cal. per Gm. mole. instead of 31,000 cal. is obtained, but the reason for this is not known.

B. DIGESTION OF COLLAGEN SUTURES BY OTHER ENZYMES

Since the same activation energy characterizes both the pepsin- and trypsin-collagen systems, it is important to know whether the same value will be obtained for other enzymes. As indicated in Figure 2 the activation energies of the collagen-enzyme system are 38,000 cal. with 1 per cent

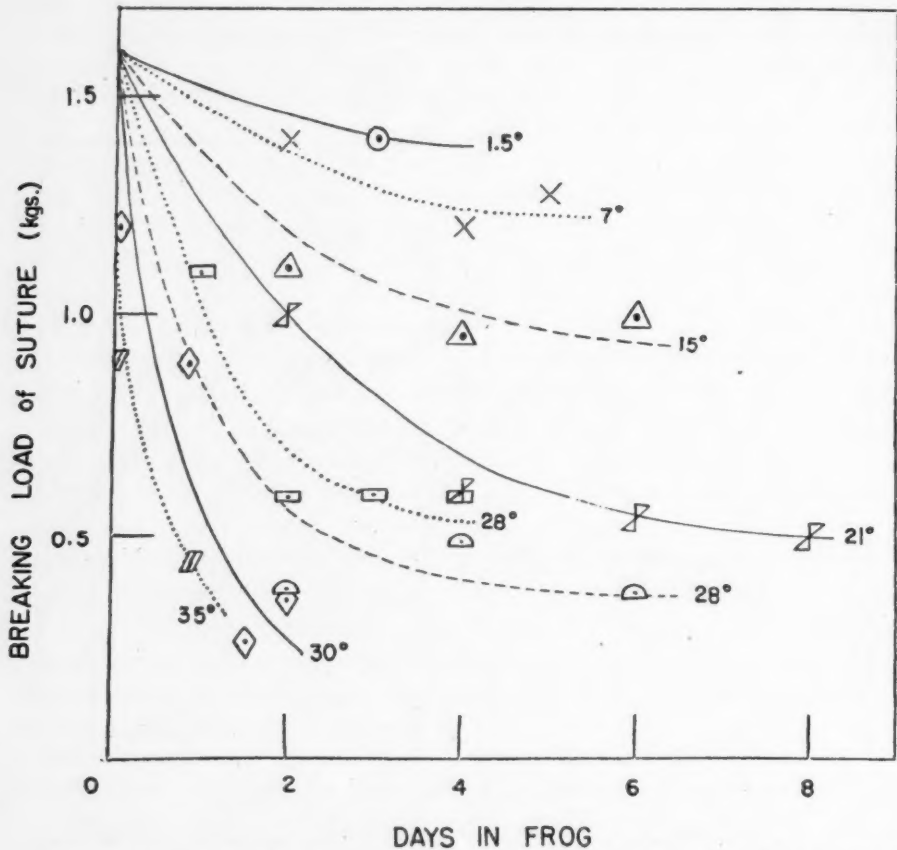


FIG. 3.—The strength (Kg. breaking load) of collagen sutures is plotted against the number of days the suture has remained in the subcutaneous tissues of frogs, which were kept at different temperatures during the experiment.

keralin (American cyanamid), 24,000 cal. with 1 per cent orthozyme (Rohm and Haas), 23,000 cal. with 0.1 per cent crystalline chymotrypsin (Lehn and Fink), and 21,000 cal. above and 44,000 cal. below 38° C. with 1 per cent papain (Merck). The results with papain are especially interesting, for it is the only known enzyme which will (although very slowly) attack native, unswollen collagen fibers. The enzyme is relatively heat stable even up to 60° C., and the papain-collagen system is characterized by one activation energy above 38° C. and another below this temperature (for similar enzyme systems, see Sizer⁸). From these experiments with several different proteases it appears that, in general, as would be expected, the activation energy

for the digestion of collagen is characteristic of the specific proteolytic enzyme used. The significance of the identity of the value for pepsin and trypsin is not known. Whether or not it is merely a coincidence must await further studies with these enzymes. The activation energy for both enzymes is different from the values reported for their action on other proteins (Butler,⁹ Sizer and Josephson,¹⁰ and Sizer⁸).

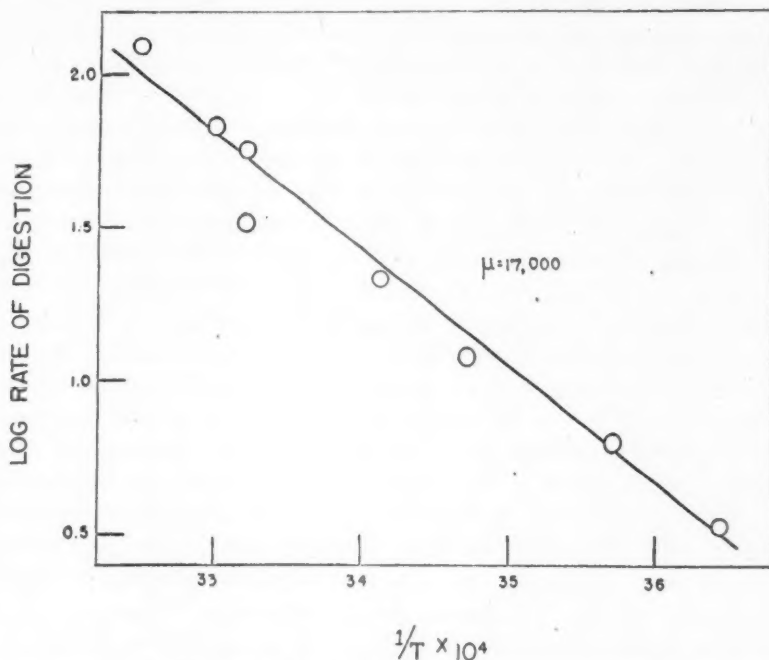


FIG. 4.—Log rate of digestion of collagen sutures implanted subcutaneously in the frog is plotted against $1/T$. The rate of digestion was taken as ten times the reciprocal of the time in days after implantation required to reduce the strength of the suture from 1.6 to 1.4 Kg. This was calculated from the curves of Figure 4.

C. DIGESTION OF COLLAGEN SUTURES IN THE FROG

The digestion and disappearance of absorbable sutures implanted in animals appears to be due to the action of tissue enzymes. Since the influence of temperature on the action of certain enzymes *in vivo* and *in vitro* appears to be the same (cf. Sizer⁸), it might be expected that the rate of digestion of the sutures would also increase exponentially with temperature in accordance with the Arrhenius' equation. From an experimental point of view the most convenient poikilothermic animal is the frog; but results which might be obtained do not necessarily depict the situation which would exist in mammals and particularly man. The winter frogs used in these experiments had been kept for several months in the laboratory without food before use. After implantation for several days many fibers broke at the point of entry through the skin instead of pulling out readily. It then became necessary to expose the suture by cutting open the skin. After the

removal of the suture, the incision in the skin was closed with surgical silk. The sutures after removal were washed and dried before testing for strength by measuring the breaking load.

When breaking load (Kg.) is plotted against implantation time in days (Fig. 3) it is apparent that at each temperature the strength of the suture decreases in a smooth hyperbolic fashion much the same as in rabbits* and in dogs (Jenkins and Hrdina¹³). The plotted points are quite scattered due to the many experimental difficulties encountered in this type of experiment. Rate may be calculated from the reciprocal of the time required to produce a given reduction in strength of the suture, *e.g.*, to reduce the breaking load from 1.6 to 1.4 Kg. The log of the rate of digestion (log 10/time in days for the reduction in strength) is plotted against $1/T$ in Figure 4. The digestion of sutures implanted subcutaneously in the frog increases exponentially with temperature in accordance with the Arrhenius' equation just as does the digestion of sutures by enzymes. The activation energy of 17,000 cal. per Gm. mole. for the digestion of sutures in the frog is different, however, from that encountered with any of the particular enzymes which have been studied. Histologic evidence suggests that the digestion of sutures implanted in animal tissues is brought about chiefly by leukocytes (Jenkins, *et al.*¹⁴). Experiments on the action of human and beef blood on the digestion of collagen sutures indicate that blood enzymes do attack the sutures. Fractionation by centrifugation of beef blood shows that most of the proteolytic action of blood is associated with the leukocytes rather than with the plasma or red blood cells. It has not yet been possible to obtain a stable preparation of proteases from leukocytes, in order to determine whether or not the activation energy for the digestion of collagen sutures by leukocytic enzymes *in vitro* is the same as that for the digestion of the sutures implanted in the tissues of the organism.

It seems significant that the digestion of collagen sutures both *in vivo* and *in vitro* increases exponentially with temperature, but since the enzymes studied are probably not the same as the ones which digest the suture in the tissue the activation energies are correspondingly different. One practical aspect of this study lies in the possible application of the results to problems of human surgery. An important problem involved in the use of catgut sutures lies in digestion of the suture before healing is completed, with the resulting opening up of the wound. It is apparent from this work on collagen and catgut (only preliminary catgut experiments have been performed with the frog) that an important factor determining the rate of digestion and absorption of sutures is the body temperature. In a patient an increased temperature of 4° C. might be expected to produce a 100 per cent increase in the rate at which absorbable sutures are destroyed in the incision if the human enzymes (or bacterial enzymes in the case of infected wounds) behave like trypsin or pepsin. If the human situation is similar to that in the frog

*Unpublished experiments by Sizer and Gould.

SUTURE DIGESTION

a rise in temperature of 7° C. will produce a doubling in the rate of destruction of the suture. In either situation, it is apparent that any elevation in body temperature may produce a marked increase in the rate of absorption of the suture. Less extensive experiments with tanned sutures (either collagen or surgical gut) indicate temperature effects on digestion similar to those for the plain sutures.

SUMMARY

The digestion of sutures of beef tendon collagen and of surgical gut by trypsin or pepsin increases in rate with temperature in accordance with the Arrhenius' equation with an activation energy of 31,000 cal. per Gm. mole. The activation energy is independent of the source and treatment of the collagen and is also independent of the purity of the enzyme preparation.

When collagen sutures are digested by other enzymes the activation energy is characteristic of the collagen-enzyme system. The activation energies are 38,000 cal. with keralin; 24,000 cal. with orthozyme; 23,000 with chymotrypsin; and 21,000 cal. above and 44,000 cal. below 38° C. with papain.

When collagen sutures are implanted subcutaneously in frogs, the rate of digestion, as measured by the rate of loss in tensile strength, increases exponentially with the absolute temperature of the frog. The activation energy is 17,000 cal. per Gm. mole. It is suggested that this value is the activation energy of the proteolytic enzyme, presumably from the white blood cells, which is responsible for the digestion of sutures in the subcutaneous tissues. It is pointed out that suture absorption in man may be greatly accelerated by postoperative fever.

The author is indebted to Doctors D. F. Waugh, T. P. Salo, and E. L. Duggan, of the Collagen Research Group at the Massachusetts Institute of Technology, for supplying the collagen fibers and for advice in the present investigation.

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THE SUBMUCOSAL MORCELLATION OF HEMORRHOIDS

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AND

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BECAUSE NEARLY EVERYONE has hemorrhoids in one form or another and because complications of hemorrhoids and hemorrhoidectomies may be very distressing, oftentimes disabling, we would like to present our preoperative, new surgical technic and postoperative care for your consideration, especially since we are aware of the fact that the methods employed in the early 1800's by the French Surgeons are still in use.¹

Hemorrhoids may occur because of straining at stool; they may follow pregnancy and they are also found in men who suffer from chronic coughs or from prostatic hypertrophy. Another cause of venous stasis is an infiltrating carcinoma of the rectum causing partial obstruction. It is, therefore, important to make a complete physical examination on all patients who present themselves for hemorrhoidal surgery. Since the present war we have seen many young men develop hemorrhoids because of altered diet, nervous tension and lack of proper toilet facilities. It was found that many of the marines and sailors became so afflicted while at the actual battle front. At one station the surgical staff averaged 3-4 hemorrhoidectomies per week, and these on boys in the 17-21 age-group.

Considering that hemorrhoids, either internal or external, are in truth "varicose veins of the rectal area" it is difficult to condone the present-day practice of "clamp and excision." The disease, being one of blood vessels primarily, there is no need for the surgeon to sacrifice large amounts of the rectal mucosa, underlying connective tissue and even muscle. An apt analogy would be to have the surgeon, who, in attempting to cure the patient of varicosities of the lower extremity, merely clamped across the varix, and excised skin, muscle and even nerves.

The present status of hemorrhoidectomy is much the same when so much healthy and uninvolved tissue is sacrificed in order to get at the offending vein. With the removal of such a large block of mucous membrane and adjacent tissue in hemorrhoidectomy, one can, without difficulty, readily explain its complications, namely, stenoses, loss of sphincter control, fissures, abscesses, not to mention pruritus and pain seen in almost every hemorrhoidectomized patient. It is altogether too common that the hemorrhoid patient dreads his operation only because he has been told about the pain and distress suffered by other patients.

Thus, realizing all this, we have attempted to correlate a technic of hemorrhoidectomy which is along anatomic lines and which attempts to preserve a normally functioning rectal tube. The result has been that the

common sequelae of hemorrhoidectomy have been reduced to a minimum and the operation itself surprisingly simplified.

Injudicious removal of tissue containing nerve filaments or even vigorous dilatation of the anus is sufficient to so harm the structures supplied by these nerves that incontinency of sphincter, proctitis, pain, and delayed healing may occur.

Therefore, considering anatomic principles, the following method of obliteration of hemorrhoids has been devised by one of the authors (H. B. B.).

Adequate preoperative preparation of the hemorrhoid patient is as important as in any other surgical procedure and contributes directly to satisfactory results, a fact which is many times overlooked. The patient is usually hospitalized the night before, having had previously a thorough physical examination and, may we stress, a complete history. Conditions predisposing to hemorrhoids are especially sought after, such as abdominal tumors, chronic bronchitis, cirrhosis of the liver, *etc.* Special examination for carcinoma must always be made prior to operation. Dr. Charles Mayo said: "I could win the office of President of the United States on the platform of free finger cots for doctors to do rectals." It is our custom to give the patient a sedative the night before, consisting of a barbiturate to allay any apprehension he might have. The perineum and anus are prepared, and three hours preoperatively the patient receives a soap-suds enema which is followed by a saline colon irrigation to remove any of the irritating qualities of the soap. A light breakfast may be given. We have found that a repetition of the barbiturate is usually sufficient as an immediate preoperative medication; however, the more apprehensive and nervous patients do require sedation with morphine and scopolamin combinations. The patient's general condition and mental make-up are the determining factors.

The anesthetic of choice is caudal block. This is given 20 to 30 minutes before the operation is to be performed. The technic employed is one commonly described; either 1 per cent novocaine or 1 per cent metycaine may be used; 30-35 cc. of solution is usually sufficient to insure adequate anal anesthesia. Local infiltration of these solutions has also been utilized with surprisingly good results.

The patient is then ready for operation. Two positions have been used, the lithotomy or Bouie, depending on the operator's choice. Thereafter, the anal area is widely prepared in the usual manner, tincture of merthiolate usually being employed, and then draped with sterile sheets. First and foremost, a careful proctoscopic examination is routinely carried out to visualize the anal canal and to inspect for the possibility of malignancy. This is best done now because of the anesthesia. At the same time, any residual foreign matter may be removed. A vigorous anal dilation is never done. It is felt that this is not necessary and may even be harmful. Many bothersome post-operative sequelae have thus been eliminated by refraining from this stretching.

No evidence of carcinoma having been found, each hemorrhoidal tag is next identified. A small linear incision, perpendicular to the axis of the

HÉMORRHOIDÉCTOMY

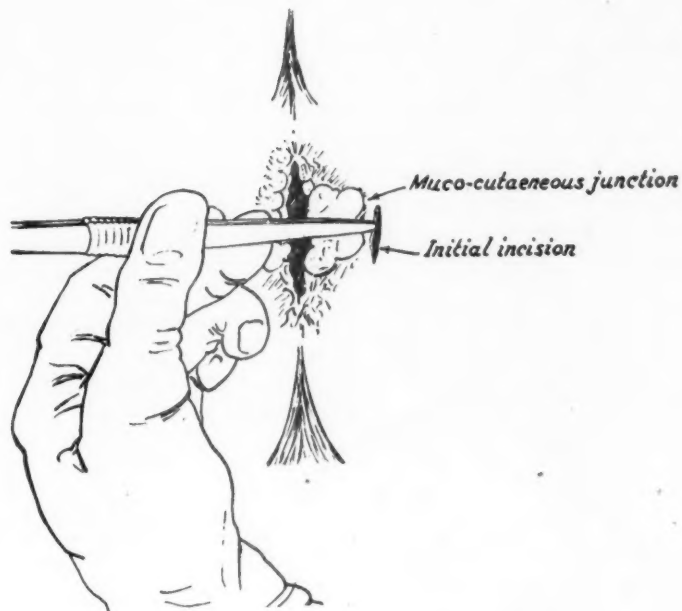


FIG. 1

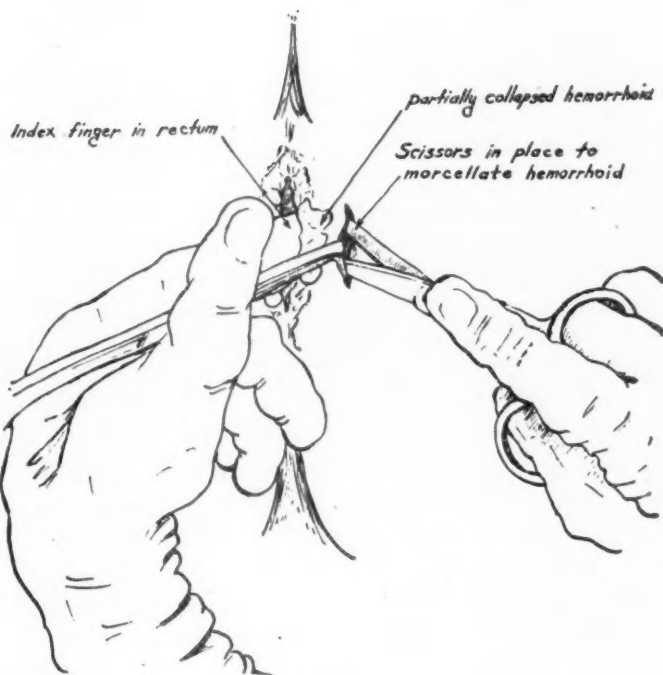


FIG. 2

rectum, is made with the knife in the skin approximately 3 cm. from the base of the first external hemorrhoid. This incision is usually just outside the pigmented area which surrounds the anus or approximately 1.5 cm. from

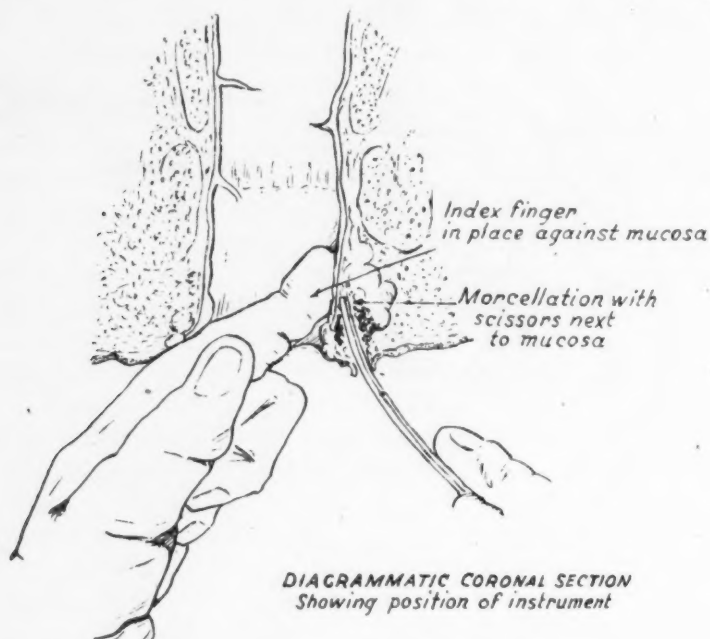


FIG. 3

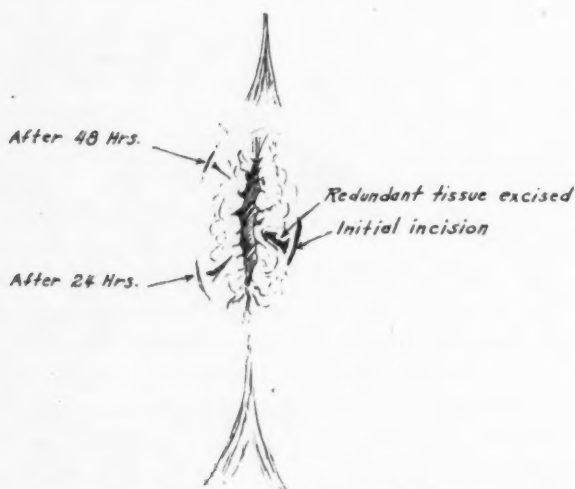


FIG. 4.—Composite sketch showing healing stages.

the mucocutaneous border (Fig. 1). Next, the medial edge of the incised skin is grasped with an Allis forceps. Holding the forceps up on the hand, the mucous membrane is dissected free from the hemorrhoid with Mayo

HEMORRHOIDECTOMY

scissors (both points dull) (Fig. 2). The dissection is then carried in like manner upwards, using the finger in the rectum as a guide until Hilton's line is reached (Fig. 3). This accomplished, the entire diseased hemorrhoidal vessel is morcellated by short bites with the scissors. If clots are present, they are removed. After complete careful morcellation, the scissors are withdrawn and any redundant, excessive mucous membrane is removed by a "V"-shaped excision (Fig. 4). It must be remembered, however, that much of this redundancy will be reduced in the process of healing. A similar procedure is carried out on the remaining hemorrhoidal tags. Thereafter, at the

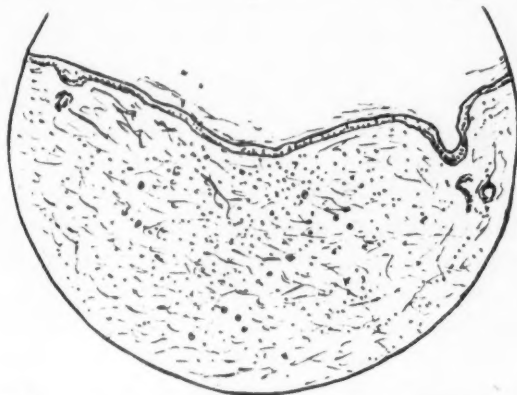


FIG. 5.—Experimental section showing intact mucosa over operated area. (72 hours postoperative)

discretion of the operator, a nupercaine-gauze pack may be inserted for hemostasis.

Scrupulous attention is also paid to the patient following the operation. On the following morning the nupercaine gauze, if inserted, should be removed. If the patient is unable to void in 12 hours, postoperative catheterization is carried out. Hot witch hazel packs have been found to be very beneficial and these applications should be started the evening of the operation. To be effective these packs must be hot. A cold and clammy pack can be very uncomfortable. Mineral oil, ounces one, by mouth, is given three times a day; fluids are given freely, with a light diet. Hot sitz baths are instituted on the third day.^{2, 3}

The operation being technically so simple, its contraindications are few. Of course, seriously debilitating disease is always investigated and no operative procedure should be carried out in such an instance. A large ulcerated mucosa would make the dissection of the mucous membrane impossible and, thus, the operation impracticable, since its continuity could not be preserved. Thrombosis without ulceration, however, is no contraindication.

In 34 consecutive hemorrhoidectomies treated by this technic, three points were outstanding: (1) Not one of these patients complained of undue pain or discomfort either during the operation or after it. The enema given on the third postoperative day was easily accomplished and normal bowel movements followed, the patients being allowed to go to the toilet. (2) Not one of

these patients suffered distention gas pains, or had to be catheterized. Normal bowel and bladder physiology was almost uninterrupted before and after the operation. (3) The speed of recovery was rapid. Two-thirds of these patients were up and about on the third postoperative day. At the end of one week complete healing had occurred in all and in most it was difficult to ascertain that the patient had had hemorrhoids. Postoperative scars or stenoses were not discernible. Five cases were encountered in which bleeding necessitated the use of rectal pack. The remainder required no packing and frequent examinations of the dressing showed only slight oozing.

In comparing our results with those of the clamp and excision or clamp and cautery methods, we are impressed by the fact that our results showed an absence of discomfort and pain, which made for a much quicker recovery and shorter convalescence. The fact that practically negligible inhibition of urination was found in these patients also was gratifying. The operation itself is anatomically fool-proof, insofar as the sphincter is not invaded, and the anal canal is not forcibly dilated either during or after. The operation not being a technically difficult one, it is relatively safe. The postoperative complications are at a minimum, and the diseased vein is completely obliterated, thus, curing the patient. The patient is further pleased at the reduction of hospitalization and the rapidity with which he is back at work. This operation was developed three years ago and, so far, we have had no recurrences in any of our cases. The patient is visibly as well as clinically cured, and has no complaints, after this type of surgical intervention.

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ALBRIGHT'S SYNDROME

REPORT OF A CASE ASSOCIATED WITH MULTIPLE PATHOLOGIC FRACTURES,
DISSEMINATED FIBROUS DYSPLASIA OF BONES, PRECOCIOUS
PUBERTY AND MULTIPLE PIGMENTED NEVI.

LT. COL. ALBERT BEHREND, M.C.,

IN 1937, Albright,¹ and his associates, called attention to a group of cases in which the symptoms were sufficiently uniform to warrant their classification as a syndrome. While individual cases had been described sporadically by various authors prior to 1937, attention became focused on them as a clinical entity by the report of Albright, so that the syndrome now bears his name.

The original article by Albright noted the following characteristic findings:

(a) Bone lesions which have a marked tendency to be unilateral and which show osteitis fibrosa on histologic examination.

(b) Brown, nonelevated pigmented areas of the skin, which tend to be on the same side as the bone lesions.

(c) An endocrine dysfunction which in females is associated with precocious puberty.

The following case fulfills all the requisites noted above and is presented in the belief that it is the thirty-fifth case to be reported in the literature. In addition to these, Gorham, and his co-workers,² list so-called "partial" cases which show some but not all of the characteristic findings. The disease remains an interesting medical curiosity since the etiology is still obscure and there is no specific therapy.

Case Report.—G. F., white female, age seven, was first seen at the Station Hospital on June 25, 1942. On June 24, 1942, she fell from her tricycle and noted pain in the right thigh which was not, however, severe. She walked into the house, but the following day was unable to bear weight on the right leg. The parents noticed some deformity of the right thigh, and she was brought to the hospital.



FIG. 1.—Demonstrating multiple hyperpigmented areas in the skin.

On admission, the patient was found to be an exceptionally intelligent and co-operative child, well developed, but with no precocious secondary sex characteristics. There were multiple small areas of dark pigmentation on the trunk (Fig. 1) and extremities, which, at the time, were not considered of unusual significance. External rotation of the right foot and ankle, with anterior bowing of the thigh, were noted, and the right leg was slightly shorter than the left. There was pain in the upper third of the femur on rotation of the leg. Roentgenologic examination disclosed a comminuted intertrochanteric fracture of the right femur. Subsequent review of the original films at the time of the second admission showed that the fracture was a pathologic one in a region of cystic bone, but this fact was not at first appreciated.

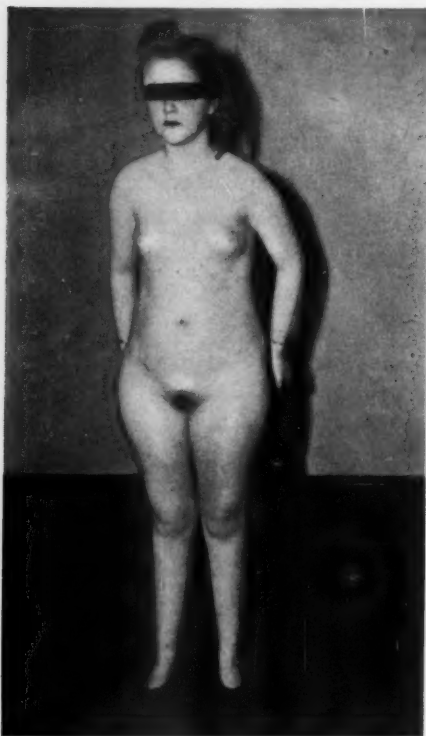


FIG. 2.—Note precocious development of secondary sex characteristics. Age: Eight years.

On June 25, 1942, under open-drop ether anesthesia, the fracture of the femur was reduced on the Hawley table and a Whitman spica of plaster of paris was applied. An excellent reduction was obtained and maintained for three months, after which the encasement was removed and weight-bearing was begun. Shortly thereafter the family moved to another post.

Second Admission.—The child was apparently well until July 10, 1943. On that date, while walking downstairs, she twisted her leg and fell. Pain in the right thigh was noted at once. Roentgenologic examination elsewhere showed marked deformity of the right hip and thigh, and there was a large bone-cyst in the subtrochanteric region, with an incomplete fracture line in the lateral wall of the cyst. Films of the lower legs showed cystic areas in the upper third of both tibiae. Films of the skull and other bones were normal.

She was readmitted to the Station Hospital on July 12, 1943. Roentgenographic findings as noted above were confirmed. Since the fracture was incomplete, and there was no shortening, a splint was not applied, but the patient was confined to bed until August 31, 1943. At this time, the fracture line had entirely disappeared, but the cystic area of bone showed little change. She

was allowed to return to her home, and it was recommended that she stay in bed for four more weeks.

Laboratory Data.—Kahn—negative. Routine urinalysis normal. Red blood cells 4,110,000, hemoglobin 90 per cent. White blood cells 8,500, polymorphonuclears 55 per cent, lymphocytes 44 per cent, eosinophils 1 per cent. Serum calcium 11.5 mg. and 10.4 mg. per 100 cc. Serum phosphorus 5.8 mg. and 5.4 mg. per 100 cc. Phosphatase 9.2 modified units. Urine calcium 284.4 mg. per vol. of 775 cc. Urine phosphorus 740 mg. per vol. of 775 cc. (24-hour specimen).

Third Admission.—The patient was readmitted to the Station Hospital October 25, 1943. Roentgenograms taken elsewhere showed increase in the area of cystic bone in upper right femur. At this time, enlargement of the breasts first became evident (Fig. 2). Also, during this admission, the patient menstruated for a period of three days.

ALBRIGHT'S SYNDROME

Questioning revealed that menstruation had occurred first at the age of three and again at the age of seven. This was the third episode of vaginal bleeding. Because of the increasing size of the bone cyst of the femur, operation was advised, and performed November 1, 1943.

Operation.—Under ether anesthesia, the right femur was exposed in the region of the great trochanter. The periosteum appeared normal but the underlying bone was pitted. The thin cyst wall was readily unroofed with a chisel and mallet. The cyst cavity was curetted. It contained fine bony spicules that formed a lacy network in



FIG. 3.—Roentgenogram showing condition of right femur at time of discharge from hospital. This leg was the site of three (3) fractures; and operation consisted of curettement of cyst and insertion of bone chips.

the cyst, and bled very freely. Multiple bone chips were taken from the shaft of the distal portion of the femur and placed in the cyst cavity. A transfusion of 250 cc. of whole blood was given during the operation.

Convalescence was uneventful until November 13, 1943, when the patient fell out of bed while asleep. Roentgenologic examination showed a complete fracture of the right femur through the region of the bone cyst, with marked angulation. On November 16, 1943, Russell traction was applied, but this had to be removed on November 19, 1943, because large blisters had developed beneath the traction tapes. On November 22, 1943, under local anesthesia, a Kirschner wire was inserted, in the supracondylar region of the right femur, and traction was applied with the leg on a Thomas splint with a Pierson attachment. The Kirschner wire was removed January 17, 1944. At this time, there was good callus at the site of the fracture and the cystic area in the bone appeared more homogeneous.

On January 17, 1944, aluminum acetate therapy was begun on the advice of Dr. Ralph K. Ghormley. This was continued until February 23, 1944, when she was dis-

charged from the hospital. At this time, the patient was sitting up in a chair but no weight-bearing was permitted.

A specimen of bone removed from the cyst at operation was forwarded for examination, but was lost in transit.

Fourth Admission.—The patient returned to the Station Hospital April 2, 1944. Her condition, in general, was good. She had not menstruated since the last admission. Her height was 60 $\frac{3}{4}$ inches and she weighed 111 pounds (50.5 Kg.). Neurologic examination was normal. Complete body roentgenograms were made at this time—the first time that this had been done since her second admission in July, 1943. The cystic area in the right femur, the site of three fractures, showed little change from

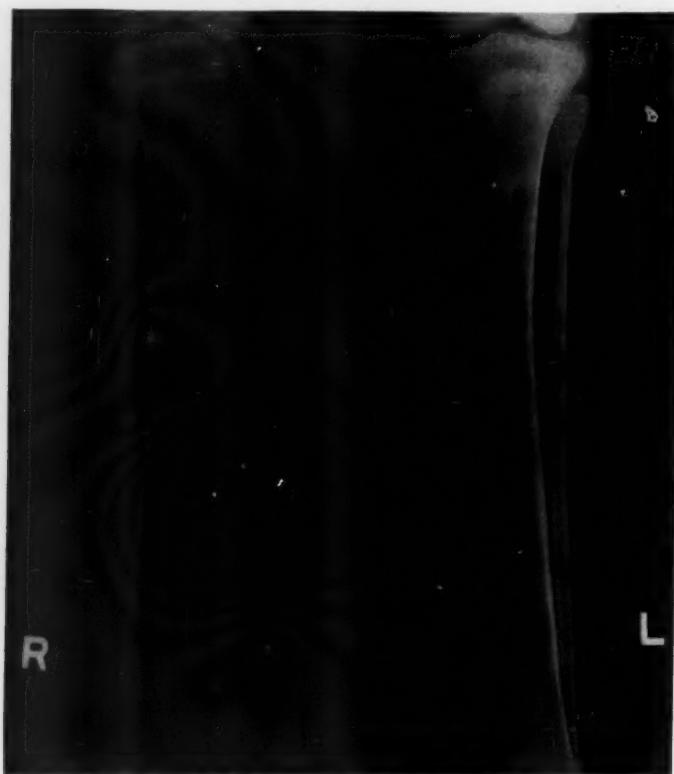


FIG. 4.—Roentgenogram of right and left legs showing cystic changes in the upper third of both tibiae and right fibula.

the previous examination in January 1944.³ The bones of the skull, including the sella turcica, appeared normal. The cystic area in the left tibia appeared to be enlarging.⁴ In addition to the right femur and left tibia, the following bones showed minor degrees of cystic change, all notably on the right side, namely, fibula, tibia, ischium, ilium, humerus, 1st metatarsal, and 3rd and 4th metacarpal (Fig. 5). The cysts involving the fibula, ischium, ilium, humerus, metatarsal and metacarpals appear to have developed since the time of the second admission—indicating progression of the disease.

Laboratory Data. Urine normal. No Bence-Jones protein present. White blood cells 7000, polymorphonuclears 68 per cent, lymphocytes 32 per cent. Red blood cells 3,770,000, hemoglobin 80 per cent. Blood cholesterol 163, phosphorus 3.5, serum calcium 9.5, and phosphatase 12.3.

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Aluminum acetate therapy was again instituted on admission. On April 4, 1944, operation was carried out on the left tibia, under light sodium pentothal intravenous anesthesia. The periosteum overlying the tibia appeared thickened and a specimen was removed for biopsy. On separating the periosteum over the cystic bone, it was noted that the cortex was already disrupted. The cyst cavity was readily unroofed with a sharp curette. The contents of this cyst was in marked contrast to that in the femur. It was soft, yellow, homogeneous and wax-like. A specimen was removed for biopsy. Bone chips from the tibial shaft (normal bone) were placed in the cyst, and the wound was closed. A small pigmented area of skin from the right thigh was also excised for biopsy. Convalescence was uneventful. The patient was allowed to leave the hospital on April 15, 1944, with instructions to continue the aluminum acetate therapy.

Histopathologic Report.—Capt. Hans G. Schlumberger, M.C.:
"1. *Curettings from bone cyst:* Section consists of fusiform connective tissue cells, occasionally arranged in bundles and whorls. About 10-12 multinucleate tumor giant cells are seen (Fig. 6) per low power field. These cells contain from 3 to 14 nuclei and have a vacuolated polychromatic cytoplasm. Foam cells are scattered abundantly throughout the section and also form isolated nests. They are very prominent in a frozen-section stained with scarlet r. (The significance of these cells is minimized by Lichtenstein and Jaffe.⁶
2. *Periosteum:* Dense, longitudinally arranged bundles of connective tissue and part cells. No inflammatory or neoplastic cell-infiltrates are present. 3. *Section of skin:* The epidermis shows moderate keratosis and acanthosis. In the basal layer are many "celles claires" having a clear cytoplasm and intimately related to adjacent nevus cells, many of which have a position and structure suggestive of Meissner's corpuscles. Masses of nevus cells are present in the uppermost layers of the corium, none have infiltrated into the deeper layers (Fig. 7). There is no evidence of malignancy.
Pathologic Diagnoses: 1. Fibrous dysplasia of bone (Jaffe). 2 Dermal-epidermal nevus."



FIG. 5.—Diagram illustrating areas of bone involvement. Note that they are predominantly unilateral.

COMMENT.—Attention was first directed to this case by the occurrence of a pathologic fracture. This was true, also, in many of the reported cases. Fibrous dysplasia of bones is a prominent feature of Albright's syndrome, and is either unilateral or predominantly unilateral. There is no general decalcification of bones as is seen in hyperparathyroidism. The epiphysis often escapes involvement, though this was not true in our case. Early union of the epiphyses is part of the syndrome, so the patients are usually of short stature.

The pigmentation is typically patchy and unelevated. It has a tendency to follow nerve trunks in some of the reported cases. Although the etiology of the disease is not known, the unilaterality of the bone lesions and the tendency of the pigmentation to follow nerve distribution together with the endocrine disorder seen in the female patients suggested to Albright that the disease was one of central nervous system origin, possibly embryonal in nature.

The syndrome is more commonly seen in females than in males. The latter do not show the precocious puberty and early maturity of secondary sex characteristics, both of which were prominent features of our case. While no

determination of sex hormones was carried out in this case, such studies in other reported cases have uniformly failed to show abnormalities.

Treatment.—No specific form of therapy is known. When pathologic fractures occur, they are treated symptomatically and usually heal readily. In our case three fractures occurred in the same area of the same bone (right femur) and all healed at least as promptly as might be expected in uncomplicated fractures.

In addition, we unroofed two of the larger bone cysts, curetted the cavities and inserted bone chips. In the case of the femoral cyst this treatment seemed to arrest the extension of the cystic involvement. In the tibial cyst sufficient time

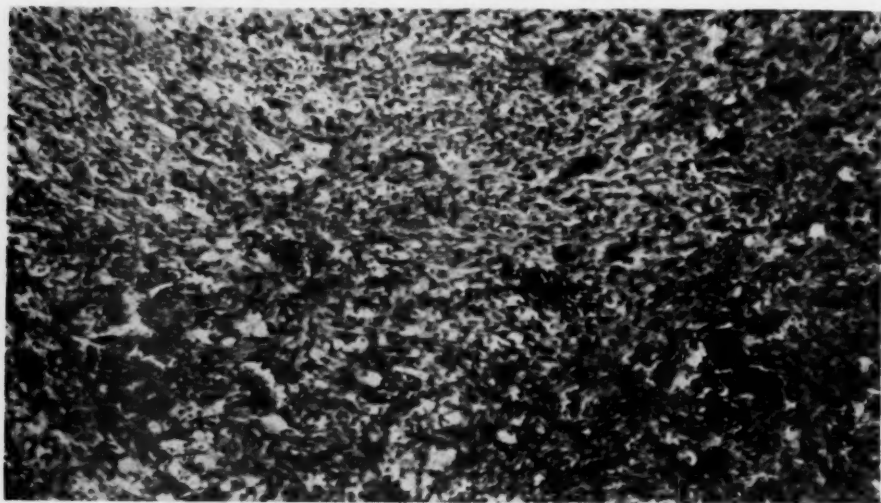


FIG. 6.—Curettings from bone cyst. Note the multinucleate tumor giant cells and fusiform cells. ($\times 120$)
U. S. Army Medical Museum. Neg. No. 79195. Acc. No. 107988.

has not elapsed to evaluate the result. We feel that operative interference is justified to obtain tissue for pathologic study for diagnosis. Insertion of bone chips appears to be of local therapeutic value.

We have also employed aluminum acetate therapy, as was done in the case reported by Dockerty, Meyerding and Wallace.³ The drug is given in the form of Burow's solution according to the formula suggested by Ghormley⁴ as follows: Sol. aluminum acetate, 150 cc.; Syr. tolu, 90 cc.; Honey q.s. ad 480 cc.; Sig. 4 cc. q.i.d., p.c.

It is recommended that at least one pint of milk a day be taken during treatment.

The use of aluminum acetate in the treatment of generalized fibrocystic disease of bone was suggested by Helfet,⁵ in 1940. The treatment is based on a concept of calcium and phosphorus metabolism, which is at variance with generally accepted ideas. Helfet postulates that parathormone controls the blood inorganic phosphate level primarily and that variations in this level secondarily affect the mobilization of calcium. Aluminum acetate provides

ALBRIGHT'S SYNDROME

ions which combine readily with phosphorus for excretion and serves to hoard calcium ions. Insufficient time has elapsed to ascertain the efficacy of this form of treatment. We can state that it has not been harmful even in doses of one dram of the prescription q.i.d. While additional cystic areas have appeared in the bones, the cysts already present have not enlarged during the period of treatment with aluminum acetate and there has, as yet, been no regression of those already established.

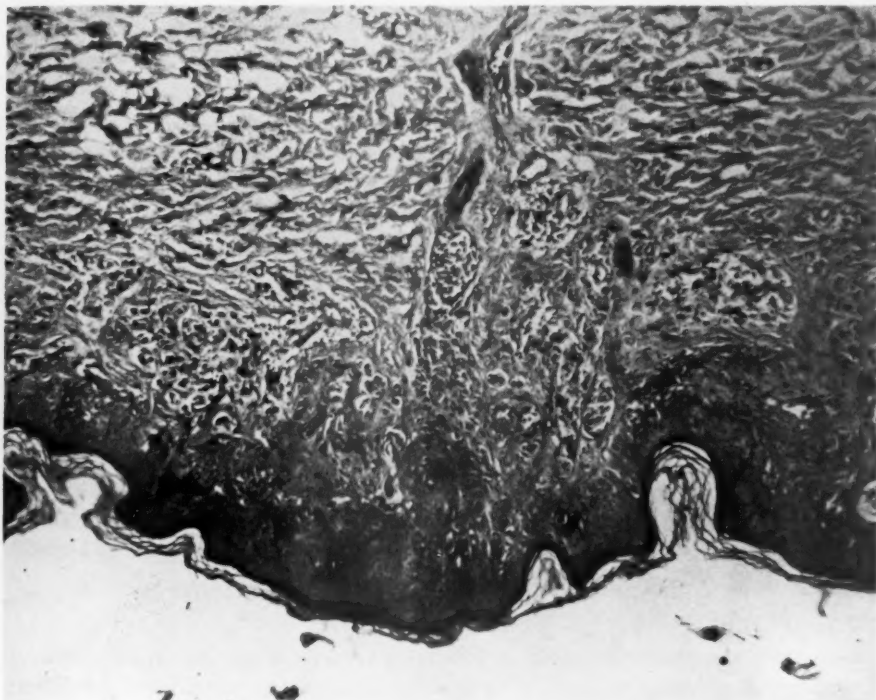


FIG. 7.—Section of skin. Section taken through pigmented nevus. There is no evidence of malignancy. ($\times 120$). U. S. Army Medical Museum. Neg. No. 79194. Acc. No. 107988.

Several reported cases of Albright's syndrome have been subjected to exploration of the parathyroid glands, despite the fact that decalcification of bones is not generalized, there is no laboratory evidence of hypercalcemia, and no tumors of the parathyroid are found at operation. Such operations can serve no useful purpose in this condition and should be avoided. Since the manifestations of the syndrome are so striking, the indications and contraindications for various forms of therapy are definite, and so little is known of the true nature of the disease we feel justified in calling attention to this additional case.

SUMMARY

An additional case of Albright's syndrome is presented. The syndrome is characterized by fibrous dysplasia of bones, with cutaneous pigmentation

in both sexes and gonadal dysfunction in females. Attention was first directed to this case by the appearance of a pathologic fracture in the right femur at the age of seven years. Two additional fractures occurred in the same area of bone in two years, and all healed well. Menstruation occurred at the age of three years for a three-day period, and the phenomenon was repeated similarly at the age of seven and eight years. Pigmentation of the skin was found to be scattered in the form of multiple small nevi, which followed no orderly distribution. Two enlarging bone cysts were unroofed, curetted, biopsies taken, and bone chips inserted. The material removed for biopsy had the gross appearance of decalcified bone spicules in the femur, and was soft, degenerated and waxy in the tibia. Response to aluminum acetate therapy has been inconclusive, but warrants further trial. Exploratory operation for removal of parathyroid glands is contraindicated. The etiology of the condition is a matter for conjecture, the treatment is empiric, and the prognosis uncertain.

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BRIEF COMMUNICATION

A SPLINT FOR INTRAVENOUS INFUSION

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THE STRAIGHT SPLINT which is generally used to immobilize the arm in the administration of intravenous infusions has been a part of our armamentarium until recently. We followed the usual procedure of immobilizing the arm on a straight board, well padded with gauze and cotton. The board was the length of the forearm and half way up the arm. The arm was stretched and tied to it with gauze. Both were then fastened to the bed. We had always been conscious of the fact that the arm during this procedure was not in the rest position, but did not know how to correct this. We felt that since the intravenous therapy was indicated and since that was the only way to give it, the patient's comfort had to be disregarded.

The immobilization of the arm with the straight splint inhibits body movements and the patient invariably complains of stiffness and cramping of the flexor muscles which progressively increases as the infusion proceeds. After the splint is removed the muscle fatigue at the elbow continues for several more hours. We thought that if the arm were in the position of slight flexion instead of full extension the patient's comfort would be increased and the complaints greatly diminished. In order to produce this degree of flexion we at first padded the protruding end of the straight splint, thus raising the forearm and producing flexion of the elbow. This method was not satisfactory because by anchoring the splint to the bed the arm lay in extension with the eventual discomfort to the patient. Of course placing the arm on a pillow would eliminate the full extension, but it would also prevent immobilization, resulting in needle displacement, with subcutaneous infiltration.

In view of the objectionable features of the straight splint it was generally felt for a long time that some modification was indicated, but the most marked incentive for the modification was the fact that one of the senior members of our staff had to receive an intravenous infusion. His discomfort, expressed in unequivocal terms, resulted in search for an improved splint. The three-angle splint which consists of three boards—a base which measures 24 inches in length, $5\frac{1}{4}$ inches in width and $\frac{1}{3}$ inch in thickness; an arm rest $16\frac{1}{4}$ inches in length, $4\frac{1}{4}$ inches in width and $\frac{1}{3}$ inch in thickness; an upright $6\frac{5}{8}$ inches in length, $5\frac{1}{4}$ inches in width, $\frac{1}{3}$ inch in thickness, and an arm extension which is a part of the base measures $8\frac{3}{4}$ inches. The upright is $5\frac{1}{4}$ inches at the base, tapering down to $4\frac{1}{4}$ inches at the upper end. The angle of the arm rest is approximately 45° . The tongues of the upright

at each end fit into the consecutive grooves of the arm rest and the base. The arm rest is attached to the arm extension by means of a dowel. The edge of the arm extension is tapered off to relieve the pressure of the splint on the upper arm. The wide base prevents tilting of the splint. The arm extension and the arm rest are covered with a mattress of leatherette; the mattress is fastened to the splint at three points; at the apex of the arm rest, at the angle, and at the end of the arm extension. Two sets of leather straps

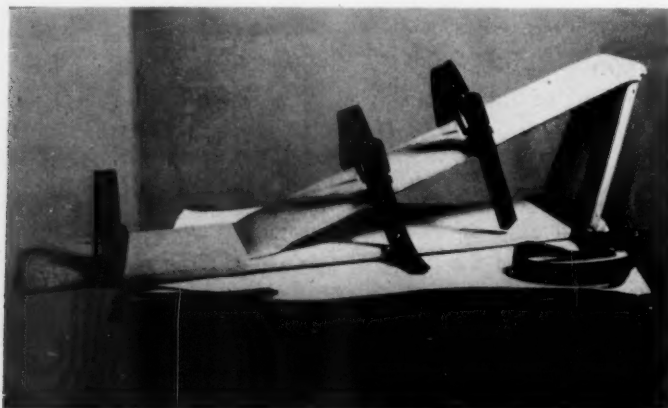


FIG. 1.—Mattress padded splint for intravenous infusions.



FIG. 2.—Lateral aspect of the splint in actual use, showing the angulation and immobilization of the arm.

with buckles are attached to the arm rest, one set to the arm extension, to immobilize the arm and the forearm. One pair is also placed at the base near the upright to fasten it to the bed.

A three-angled splint which is covered with a mattress and leather straps is ready for intravenous infusion at a moment's notice. This is not the case with the commonly used straight splint. There is much lost motion in its preparation. The nurse or doctor has to prepare the splint by padding it with cotton and wrapping it with bandage. This preparatory procedure consumes much valuable time which is actually wasted, since the padding can be

INTRAVENOUS INFUSION SPLINT

used for the one patient only and must be discarded before repadding the splint for the use of the next patient. Then the nurse spends time in bandaging the arm to the splint and the splint to the bed. The loss of time and the wasting of material is completely eliminated with the use of our splint, since its application is instantaneous.

In patients with small, deep-seated veins it may be more advantageous to introduce the needle before immobilizing the arm. Of course if a vein in the forearm, wrist, or back of hand is used, this splint offers added advantages.

The length, the width and the thickness of the splint do not necessarily have to be measured to the tenth of an inch—we are simply stating the exact measurements of our splint. The length of the arm rest and arm extension may be about 26 inches, so that the greatest part of the arm and forearm in the adult come to rest upon it. To accommodate the younger patients the base board would have to be proportionately less in length. The upright should be six to seven inches, in order to form about a 45° angle. The dowel, tongue and groove are only a mechanical finesse. Ordinarily, simple nailing of the parts will suffice. The mattress and leather straps were added to eliminate the repeated use of cotton and gauze, as a time-saving device, and also as a sanitary precaution. The mattress may be covered with oilcloth, thick cellophane, or any other waterproof material which can easily be cleansed of blood and other fluids.

If a mattress is not desired, the planed and waxed wooden angular splint when covered with one layer of gauze provides sufficient padding for the resting arm. The advantages of this splint as we have found it in actual use are as follows:

- (1) It is ready for instantaneous use.
- (2) The cramping and stiffness of muscles are reduced to a minimum—much appreciated by the patients.
- (3) It takes the weight off the forearm, thus reducing the muscle fatigue after removal of the splint.
- (4) Patient has more freedom of action and can turn from side to side.
- (5) It is easier to fasten the arm to the splint and the splint to the bed for complete immobilization.
- (6) The leather straps immobilize the arm and the forearm, thus eliminating the constant addition of gauze in a given case.
- (7) The mattress eliminates the repeated padding with cotton and gauze with each successive infusion. It is a time-saving device.
- (8) In our hands we found that the use of this splint tends to make an intravenous infusion an exact, clean, comfortable, economical and time-saving procedure.

BOOK REVIEW

HYPERTENSION AND HYPERTENSIVE DISEASE. By William Goldring, M.D., and Herbert Chasis, M.D. New York, The Commonwealth Fund (1944).

Doctors Goldring and Chasis' book is a brief but thorough discourse on a subject around which an enormous literature has grown. In clear, concise and simple language the authors encompass the field of hypertension and related nephritis from their point of view. It is their thesis that hypertension presents a so-called malignant phase only because of nephrosclerosis. Accordingly, the clinical term "malignant hypertension" is mentioned. The surgical aspects of hypertension, including the operations of sympathectomy and splanchnicectomy, are treated briefly. On the other hand, there are great details in the appendices for a student of the subject in its nonsurgical aspects. The book provides an excellent approach to the subject for the student and the physician.

HAROLD NEUHOF, M.D.

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